Clinical Approaches to Hospital Medicine

Advances, Updates and Controversies

Kevin Conrad
Editor

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Preface

Welcome to Clinical Approaches to Hospital Medicine. I extend my gratitude to the chapter authors and especially to the managing editor, Theodora Valovska who made this text possible.

This book provides an update on recent clinical practice and an in-depth view of selected topics relevant to the practice of hospital medicine. It is divided into four sections that explore clinical issues, system issues, future trends, and ethical issues. Both American and international authors were selected not only for their expertise in clinical medicine but also for the diversity seen in the practice of hospital medicine.

Hospital medicine continues to be a thriving specialty but is no doubt experiencing growing pains as it enters its third decade. Rapid growth has led to problems of retention, burnout, and overexpansion of practice scope. In this environment, the specialty is increasingly being called upon to further define itself, prove its value, and develop a template for future expansion. Unbridled enthusiastic growth and expansion has been replaced by some degree of introspection.

I have been part of a program that began in the early days of hospital medicine. In the past 20 years since its formal inception, hospital medicine has grown to nearly 50,000 practitioners. No specialty has come so far so fast. The original intent of our own hospitalist program was to provide stability to our house staff teaching program. This has continued to be a major component of hospitalist programs around the country, but the practice has endeavored to do so much more. Additionally, programs have also been called upon to comanage surgical patients, provide cost-effective services, provide perioperative services, and lead quality initiatives.

Perhaps the most important section is the one dedicated to the opioid epidemic. Hospital medicine is being called upon to not only respond to the pressing needs of the epidemic but to also provide leadership. Hospitalists are well suited to respond to an epidemic that crosses all specialties. As leaders, it is important that we develop a fundamental understanding of the pathophysiology, background, and system issues as we take on this complicated task.

The last section provides an overview on the state of hospital medicine both here in the United States and internationally. I think it is important that all hospitalists

have basic understanding of practice patterns from both here and abroad. The final chapter explores the practical application of philosophical tools in our daily practice. In a specialty that deals with death on an almost daily basis, these tools are needed to assist us in our personal struggles to work in a challenging environment.

Now more so than ever, it is important that we define what we do, do it well, and communicate our value to the healthcare system. We hope that this first edition text helps to explore what we have accomplished and what challenges we will face in the future. We hope to receive your feedback in improving future editions. Please share your thoughts on what topics you thought were significant and what should be included in future editions.

New Orleans, LA, USA Kevin Conrad

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This text was possible by the insights and hard work of the managing editor Theodora Valovska. Her efforts to collaborate with a wide a variety of chapter authors was key in the development of this book.

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Part I
Clinical Updates in Hospital Medicine

With this section of the text, we aim to cover some of the more frequently encountered pathologies, and explore their most up-to-date management. Congestive heart failure, pneumonia, delirium, and cellulitis remain a significant part of the practice of hospital medicine, accounting for the majority of admissions in many hospitals across the US. These topics are explored with an emphasis on new treatment methods.

Not only are US Candidemia rates increasing over the past 20 years, some strains of *Candida* are becoming increasingly resistant to first and second line antifungal medication [1]. Thus, we have included a chapter on the impact of *Candida* and the current development of effective treatment regiments.

Early diagnosis and treatment of sepsis is a focus of not only hospital medicine, but across all specialties. Sepsis remains one of the most expensive in-patient hospital conditions [2]. Diagnostic tools and treatment algorithms have greatly improved our approach to treating sepsis in the past decade. These tools continue to evolve to determine who best benefits from early aggressive goal directed therapy. The sepsis chapter explores the evolution from SIRS to SOFA in the diagnosis of sepsis.

1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004;39(3):309–17.
2. Pfuntner et al. Costs for Hospital Stays in the United States. HCUP Statistical Brief #168.

Chapter 1
Diagnosis and Treatment of Heart Failure for Inpatient Providers

Hamang Patel and Amanda L. Bennett

Introduction

Heart failure (HF) affects more than 5.7 million adults in the United States and current projections estimate the prevalence of HF will continue to increase [1]. Accounting for more than 1 million admissions annually, HF is the leading cause of hospitalization among the Medicare age group with an overall 1-year mortality rate of 29.6% [2]. In 2013, total cost for HF was estimated to be $30.7 billion with 68% being attributable to direct medical costs. Projections show that by 2030, the total cost of HF will increase almost 127% to $69.7 billion with an estimated $244 spent annually for every US adult [3]. As an emerging issue in hospital care, the hospitalist provider can anticipate a large portion of admissions with either primary or comorbid HF.

In this article, we will discuss:

- How to recognize HF and classify accordingly
- Key treatment modalities
- When to consult subspecialists
- Risk factors for re-admission and strategies for prevention

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Epidemiology

The incidence of HF approaches 10 per 1000 population after 65 years of age [4]. HF incidence rates in men double every 10 years from 65 to 85 years for men and triple for women [5]. Incidence rate per 1000 person-years is lowest among white women and highest among black men with a disproportionate prevalence in the non-Hispanic black population [6]. 5-year survival rates are 97%, 96%, 75%, and 20% for stage A, B, C, and D respectively [7].

Risk factors for HF include: CHD, cigarette smoking, hypertension, obesity, diabetes, dietary sodium intake, and valvular heart disease [8]. Hypertension and tobacco use are among the most important modifiable risk factors. Racial disparities between diagnosis, treatment, and mortality are significant.

HF is the leading cause of hospitalization in the Medicare age group, and has a significant risk for readmission in the 30-day post-discharge window. After initial HF diagnosis, 83% of patients are hospitalized at least once and 43% are hospitalized at least four times with more than half of these hospitalizations being related to non-cardiovascular causes [6]. Readmissions also constitute a significant financial and quality of life burden for these patients. Consequently, the Centers for Medicare and Medicaid Services financially penalize medical institutions for HF readmissions.

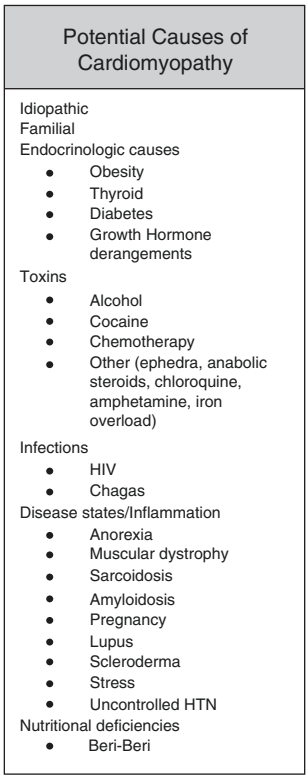
Recognizing Established Heart Failure in the Hospitalized Patient

The phenotype of clinical HF has many different instigating factors (see Fig. 1.1). A wide variety of complex medical conditions may lead to the initial presentation of a patient with HF at nearly any age. Similarly, many medical conditions may mimic HF. It is also important to note that HF is a progressive disease; consequently, early detection and treatment is crucial to prolonged survival and reduced morbidity. In patients with known HF, typical precipitant factors include medication non-adherence/failure to optimize, dietary indiscretion, new ACS, arrhythmia, and exacerbations of other comorbid conditions.

Presentation

HF has a wide and highly variable presentation (Fig. 1.2). Irrespective of acuity or epidemiology, the most common presenting complaints of HF exacerbations include dyspnea and fatigue. Patients may notice limited exercise or activity tolerance and fluid retention in the form of central or peripheral edema; however, in the setting of acute onset HF these symptoms may not yet be present. Many patients will note an increase in weight and/or difficulty lying flat. Patients may present with or without

Fig. 1.1 Potential causes of cardiomyopathy. Disease states which may cause cardiomyopathy and consequently lead to signs and symptoms of heart failure. *HIV* human immunodeficiency virus, *HTN* hypertension



Classic review of systems in heart failure	Classic physical exam findings in heart failure
Dyspnea on exertion	Edema or ascites
Fatigue	+/- New murmur
Shortness of breath	S3/S4
Reduced exercise tolerance	Crackles
Edema or leg swelling	Pleural effusion
Rapid weight gain	JVD
Orthopnea	Displaced PMI
Palpitations	Hepatomegaly
Chest pain	Weight gain
Non-productive cough	

Fig. 1.2 Presentation of heart failure. Classic symptoms and physical exam findings found in heart failure exacerbations. *JVD* jugular venous distention, *S3/S4* cardiac gallops, *PMI* point of maximal impulse

signs or symptoms of volume overload. The clinical index of suspicion for HF should be raised in patients with confounding presentations or who were previously identified as having alternate diagnoses but are non-responsive to treatment. The ultimate diagnosis is achieved through a combination of history, physical exam, and supplementary diagnostics.

History and Physical Examination

Historical evaluation should include duration of symptoms, severity, symptoms of ACS, recent or prior hospitalizations with similar symptoms, medication, and diet adherence. Physical examination should include BMI and weight gain/loss evaluation. Detailed cardiac auscultation should be performed to assess for aberrant rhythm, extra heart sounds, or murmurs; size and location of point of maximal impulse. The cardiac exam should also detail orthostatic blood pressure, jugular venous pressure at rest and after compression, presence of edema or abdominal distention, temperature of lower extremities, and capillary refill times. Each patient should receive a detailed pulmonary exam for rate, rales, effusions, or signs of infection. Abdominal exam may yield hepatomegaly and/or ascites.

Evaluation and Pertinent Studies

Evaluation of a suspected or known HF patient should involve a systematic identification of and ruling out of possible precedent and contributing comorbidities (Fig. 1.2). In this section, we will discuss initial and supplemental serologic testing, as well as imaging modalities that are currently recommended for patients with HF. These studies are used to determine the etiology and subsequent treatment pathways a provider may take to stem or potentially reverse a patient's HF. Medical evaluation should seek to identify which of the general categories of HF precipitants. These categories include:

- ACS
- Tachycardia/arrhythmia
- Valvular disease
- Endocrine and metabolic Causes
- Worsening or uncontrolled comorbid conditions
- Toxins
- Infections
- Other disease states or causes for inflammation

Initial evaluation of suspected or decompensated HF (Fig. 1.3) should include 12-lead ECG, chest X-ray, complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone [6]. B-type natriuretic peptide is considered the gold standard for biomarker indication of HF and will be discussed in a later section. Serial monitoring of these studies is recommended when indicated.

When clinical suspicion is present, diagnostic testing for rheumatologic disease, amyloidosis, or pheochromocytoma is recommended. The provider should seek out additional testing for relevant precipitants of cardiomyopathy and subsequent HF as

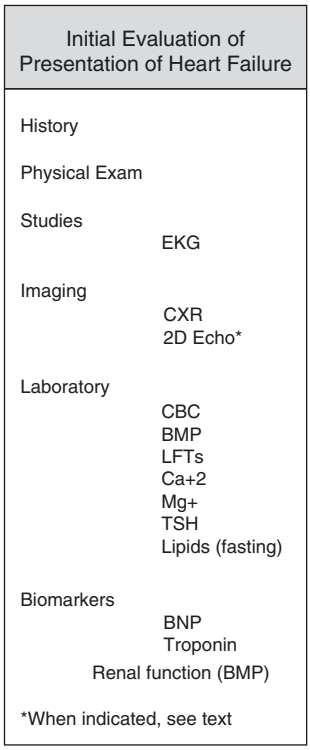


Fig. 1.3 Initial evaluation for presentation of heart failure. Initial recommended evaluation for patients presenting with signs and symptoms of heart failure. *EKG* electrocardiogram, *CXR* chest X-ray, *CBC* complete blood count, *BMP* basic metabolic panel, *LFT* liver function tests, *TSH* thyroid stimulating hormone, *BNP* B-type natriuretic peptide

they pertain to the individual patient social situation. For all cause HF, documentation of LVEF is a quality-of-care performance measure and should be performed by the most prudent imaging modality available [9].

Biomarkers: Classic and Emerging Markers

As part of the initial clinical evaluation, various biomarkers may be used to reinforce diagnosis, derive prognosis, and provide targets for treatment in HF. Depending on the biomarker selected, lab results can be obtained to reflect portions of potential pathophysiologic aspects of the HF disease process. Key areas of biomarker detection involve assessment of myocardial wall stress, inflammation, myocyte injury, neurohormonal upregulation, and myocardial remodeling [10]. Of the multitude of biomarkers available to the practicing clinician, the ACCF/AHA only currently recommends routine assessment of natriuretic peptides and cardiac troponin. Laboratory assessment of natriuretic peptides, myocardial necrosis, infection, and/or renal insufficiency is cost-effective and readily available. It should be noted that the combination of multimodality biomarker assessment is an active area of HF research and may lead to the development of sophisticated risk stratification tools in the future.

Natriuretic Peptides

Produced by cardiomyocytes under many circumstance, B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are classically regarded as markers of myocardial stretch. These biomarkers are helpful in establishing the presence and severity of HF in times of clinical uncertainty. Used interchangeably, there is little to be gained by ordering both of these markers of myocardial stretch and providers should utilize whichever marker is more readily available at their institution.

Elevated levels of either BNP or NT-proBNP while sensitive for HF are not specific. Other potential cardiac causes of elevated natriuretic peptide markers include but are not limited to ACS, valvular heart disease, diseases of the pericardium, atrial fibrillation, myocarditis, cardioversion, and recent cardiac surgery. Potential non-cardiac causes of elevated natriuretic peptides include anemia, renal failure (acute or chronic), critical illness, severe burns, chemotherapy, obstructive sleep apnea, pulmonary hypertension, and pneumonia [6]. It is also important to remember that particular clinical factors of the patient, such as obesity, may create falsely low natriuretic peptide levels and thusly these tests should be used to support a clinical picture and not as absolutes.

The ACCF/AHA does not recommend treating patients to a target natriuretic peptide level as this has not established a clear benefit in the HF population [11]. However, the addition of natriuretic peptide biomarkers for diagnosis/exclusion of HF as well as prognosis for patients with HF in the hospital setting is recommended.

Cardiac Troponin T or I

A marker of myocardial injury and ischemia in patients with known CAD, cardiac troponin elevations in HF are associated with worse clinical outcomes and mortality [12]. The ACCF/AHA formally recommends routine assessment of troponin levels on presentation of any patient with suspected or decompensated HF. In the setting of chronic HF, those patients who demonstrate a decrease in troponin levels as a result of GDMT have statistically significant improvements in prognosis [13]. Thus, assessment of troponin may be useful to uncover the etiology of a new HF presentation and can be used as a predictor of clinical outcomes. In addition to formal assessment, current guidelines recommend the addition of troponin assessment for additive risk stratification for patients with HF in the hospital setting.

Soluble ST2 and Galectin-3

While still relatively obscure outside the realm of Cardiology, the use of soluble ST2 and galectin-3 to determine the presence and degree of myocardial fibrosis has shown promise as a collection of biomarkers capable of producing a meaningful prognostication for hospitalization and death in HF patients [14]. Of the two, ST2 shows superior

predictive qualities over galectin-3 [15]. Galectin-3 is more closely associated with renal insufficiency than hemodynamic indices [16]. These markers currently have a IIb level of recommendation as they pertain to risk stratification in the setting of HF.

Other Important Biomarkers in the Hospital Setting

Many other biomarkers are becoming more readily available but have yet to reach sufficient studies or demonstrate significant accuracy or specificity to HF. Although they do not carry guideline levels of recommendation, markers such as procalcitonin and assessment of renal function are frequently available and easily interpreted. These markers may also be of additional help in periods of clinical uncertainty particularly in patients with multiple comorbidities. Assessing these markers may assist providers in the diagnosis and management of a patient with HF on the diagnostic differential.

Procalcitonin

As dyspnea is one of the predominant physical complaints that may trigger suspicion for HF, it may prove useful to the clinician to obtain a procalcitonin level to distinguish between etiologies [17, 18]. Procalcitonin is commonly known as a biomarker of infection, but it may also be useful in discovering non-occlusive mesenteric ischemia associated with recent cardiac surgery or decompensated HF [19]. Providers should be cautious to correlate patient presentation, symptoms, and history when using this biomarker.

Renal Insufficiency

Assessment of renal function and markers or renal injury can provide insight into prognosis for patients with HF. Renal and cardiac function are intimately associated in HF and a decline in renal function may be a precipitant of HF progression or a result of progressive cardiac function decline [20]. Worsening or high BUN/Cr levels during hospitalization have a poorer prognosis and may affect the ability of patients to remain on GDMT or symptomatic therapies.

Imaging

Chest X-ray Findings

X-ray imaging of the chest is recommended to assess the heart size and assess for presence of pulmonary congestion in patients with suspected or new-onset HF. Such imaging may prove helpful in ruling out alternate causes for presenting

symptomatology. In HF, findings may range from no abnormalities—often in the acute HF setting such as viral or toxic myopathies—to enlarged cardiac silhouette, pulmonary edema, cephalization of the pulmonary vasculature, and even pleural effusions.

Echocardiography

2-dimensional echocardiography (2D-echo) with Doppler should be performed on the initial evaluation of a patient presenting with HF [6]. This non-invasive test is relatively cost effective and readily available at most hospitals. As an imaging modality, 2D-echo allows for accurate assessment of ventricular function which may portend further prognostication or possible treatment modalities. Per the ACCF/AHA guidelines, repeat assessment of EF is only indicated if the patient has had a significant change in clinical status, who have recently recovered from clinical events, or who have received GDMT that may have a significant impact on cardiac function. Repeat imaging is also indicated prior to assessment for device therapy.

MRI/Radionucleotide Scan

Cardiac MRI is a complementary non-invasive imaging modality for the assessment of myocardial ischemia and viability. MRI is particularly helpful in the assessment of myocardial scar burden or in those situations with myocardial infiltrative process. Both MRI and radionucleotide scans are effective studies in EF assessment or volume when 2D-echo is insufficient [21].

Diagnosis of New Onset Heart Failure

After performing the above recommended testing, an assessment of the etiology of HF must be performed. Treatment and management of HF branches into different trajectories based on ischemic or non-ischemic profiles. Therefore, it becomes important to accurately assess if ischemia is the cause of presenting or worsening symptoms. Per the ACCF/AHA guidelines, coronary angiography is indicated in patients with known CAD and angina or with significant ischemia on ECG or non-invasive testing demonstrating impaired ventricular function [22]. Angiography should only be performed in patients who are potential candidates for revascularization. If CAD can be excluded as an etiology of HF, current guidelines do not recommend angiography evaluation. It should be noted that many disease states may mimic HF; consequently, it is important to rule out alternative causes for phenotypic HF as treatment patterns may differ. For more information of disease states that may mimic HF, please see the 2013 ACCF/AHA guidelines for diagnosis and management of HF.

Clinical Assessment of Heart Failure

Severity

Management of HF is dependent on ACCF/AHA stage (see Fig. 1.4a, b). Staging of HF is helpful to document the overall progression of a patient's disease. Etiology and symptoms are not part of this classification system. The stages represent (A) patients at risk for HF, (B) patients with structural heart disease but no symptoms,

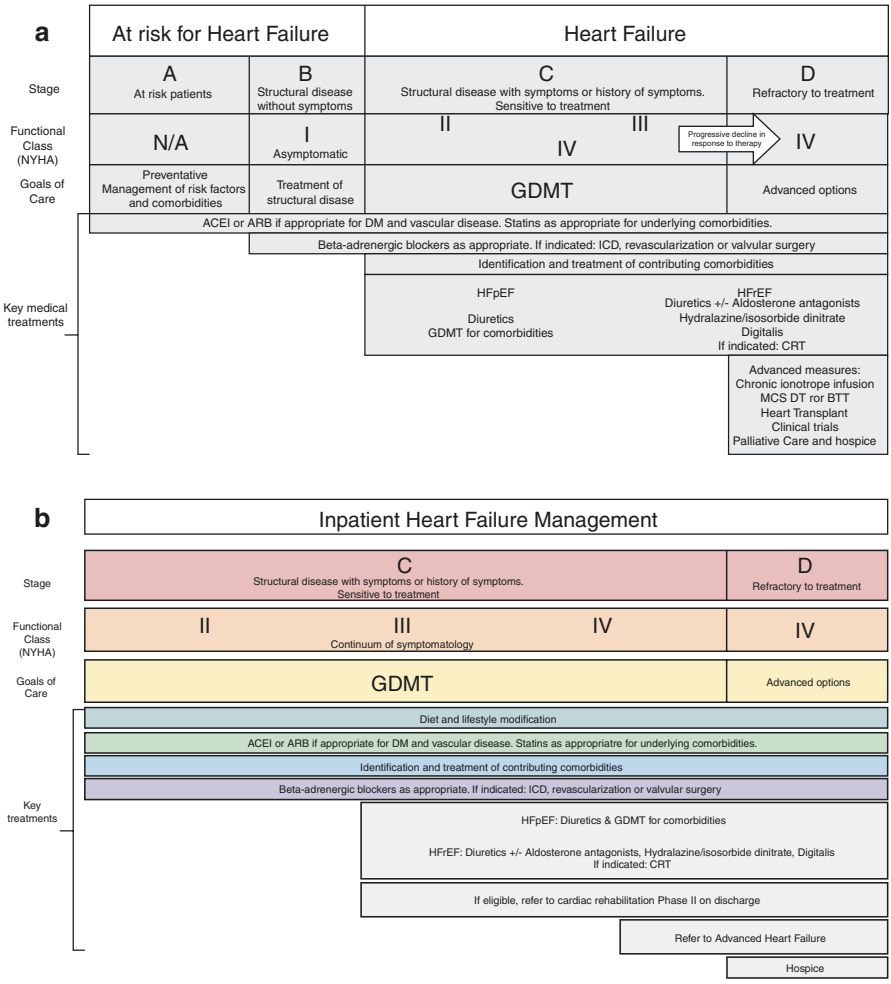


Fig. 1.4 (**a**) Staging, classification, and recommended management of heart failure. (**b**) Staging, classification, and recommended management of inpatient heart failure. *NYHA* New York Heart Association, *GDMT* guideline-directed medical therapies, *ACEI* angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blockers, *ICD* implantable cardiac defibrillator, *HFpEF* heart failure with preserved (>50%) ejection fraction, *HFrEF* heart failure with reduced (<40%) ejection fraction, *CRT* cardiac resynchronization therapy, *MCS* mechanical circulatory support, *DT* destination therapy, *BTT* bridge-to-transplant

(C) patients who are responsive to GDMT but have structural disease with symptoms or a history of symptoms, and (D) symptomatic disease that is unresponsive to GDMT. Those patients with stage D heart failure are considered to have advanced heart failure and are often cared for by advanced HF specialists. Both patients with reduced EF (HFrEF) and preserved EF (HFpEF) are represented by these stages.

Symptoms

A patient's NYHA HF classification (see Fig. 1.4a, b) is a subjective assessment designed that is representative of current symptoms. Patients may progress through the classes, have combination of classes or rapidly fluctuate between classes. Appropriate assessment of the HF patient involves determining the patient's baseline NYHA class and comparing it to their presenting class. Symptoms range from asymptomatic (class I) to severely symptomatic (class IV). NYHA classification is considered an independent predictor of mortality [23].

Function

Heart failure management and therapies are stratified by EF. The vast majority of clinical trials and studies that guide HF treatment were conducted on patients with reduced ejection fraction (HFrEF). HFrEF definitions vary but the ACCF/AHA guidelines define HFrEF as an EF <40%. Preserved EF (HFpEF) is HF symptoms with an EF >50%. EF between 40 and 50% is considered an intermediate group.

Management

Initial management is dependent on ACC/AHA stage and EF assessment (see Fig. 1.4a, b). Further management and titration of medications is augmented by NYHA stage. Each additional therapy should be additive to the prior and build in a stepwise fashion that is tailored to unique physiology, race, and comorbidities of each individual patient. All patients, regardless of stage or GDMT should receive daily weight monitoring, strict monitoring of input and output, as well as daily assessment of renal function and electrolytes. Below are the general categories of interventions and medications used in HF. It should be noted that abrupt or inappropriate change of medical therapy in the acute setting may worsen outcomes or prolong hospital stay. If any medication is held during a hospitalization, it should be restarted before hospital discharge if tolerated.

Preventative Management of Risk Factors and Comorbidities

Regardless of EF, mitigation of known risk factors and GDMT management of comorbid conditions applies to patients with HF. If other medications such as statins or anticoagulation are recommended for the treatment of any comorbidity, then these are indicated in HF but should not be initiated for HF disease alone.

Avoidance of Medications that May Cause Harm

Medications that are known to cause harm in the setting of HF include but are not limited to calcium channel-blockers (CCBs), NSAIDs, thiazolidinediones, and many antiarrhythmic medications. Providers should defer to advanced specialists for co-management of arrhythmias when necessary. Of the CCBs, amlodipine is recommended for management of comorbid hypertension or ischemic heart disease as this medication has demonstrated neutral effects on HF morbidity and mortality [24].

Treatment of Structural Disease

Structural diseases should be corrected and/or managed per current guidelines in the setting of both HFrEF and HFpEF.

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The cornerstone of HF therapy has been the suppression of pathologic renin-angiotensin-aldosterone system (RAAS) alterations. ACEI and angiotensin receptor blockers (ARBs) are recommended for all patients with HFrEF and as comorbidity management when appropriate in HFpEF. These medications are not indicated for HFpEF without appropriate comorbidity. In the acutely hospitalized HF patient, it is reasonable to hold, discontinue, or reduce ACE/ARB therapy in the setting of worsening renal function.

Combination ARB-Neprilysin Inhibitors

Combination ARB-neprilysin inhibitor (ANRI) therapy has recently proved to have significant mortality reduction in HF. Neprilysin inhibitors upregulate the protective neurohormonal system of the heart which has shown significant benefit in those able

to tolerate the additional therapy [25]. Transition from ACE/ARB therapy to ANRI therapy is a reasonable strategy in class II or III who are otherwise optimized on GDMT [26].

Beta-Adrenergic Blockers

Use of either bisoprolol, carvedilol, or sustained release metoprolol succinate is recommended for patients with HFrEF. These medications are proven to reduce mortality in HF with or without CAD or diabetes. Beta blocker (BB) therapy should be initiated upon diagnosis of HFrEF. In patients with known history of fluid retention, initiation of BBs is associated with an increased incidence of fluid retention and should be accompanied by initiation of diuretics.

Aldosterone Receptor Antagonists

In patients with LVEF <35% and NYHA class II-IV HF, aldosterone receptor antagonist (ARA) therapy is recommended. ARAs are also indicated for patients in the acute post MI period with LVEF <40% and new HF symptoms or have a history of diabetes. Provided the serum potassium is <5.0 mEq/L and creatinine is <2.5 mg/dL in men or <2.0 mg/dL in women, initiation of ARA therapy has been shown to reduce morbidity and mortality in HF [27]. For patients that are acutely hospitalized with declining renal function, it is reasonable to adjust ARA therapy until renal function improves.

Hydralazine and Isosorbide Dinitrate

For those patients with NYHA class II-IV HFrEF and are self-described African American, addition of hydralazine and isosorbide dinitrate is indicated once patients are on maximally tolerated ACE/ARB and BB therapy. Arterial vasodilation with hydralazine combined with venodilation using isosorbide dinitrate may help reduce HF symptoms and comorbid HTN by reducing afterload and preload [28].

Digoxin

Useful for decreasing hospitalizations and occasionally for control of arrhythmias, initiation of digoxin may be utilized for patients with HFrEF. Regardless of the underlying rhythm, ability to tolerate GDMT or cause of HF, digoxin has been

shown to improve quality of life and reduce symptoms [29]. This medication should be used with caution in patients with reduced renal or hepatic function as the therapeutic window is narrow [30]. Discontinuation of digoxin may be required if patients experience symptomatic bradycardia or other signs or symptoms of toxicity.

Diuretics

Loop diuretics are indicated for all volume overloaded patients NYHA class II-IV. In the outpatient setting, self diuretic titration is an essential component of self-care and all patients should be educated on appropriate triggers to seek medical attention. For hospitalized and symptomatic HF patients, intravenous loop diuretics should be initiated at doses that are equal to or in excess of any chronic daily therapy. Use of pulse or continuous infusion is indicated, and clinic studies have found no significant difference between these two methods in terms of symptoms, effect of diuresis, or clinical outcomes [31].

Cardiac Rehabilitation

Effective cardiac rehabilitation (CR) is a fundamental component of HF management for ambulatory patients with stage C HF with NYHA functional class II or III. Both the AHA and ACC recommend CR at the Class I level. Contraindications for CR include unstable HF, uncontrolled comorbidities (diabetes, hypertension, pulmonary pathology), symptomatic aortic stenosis, or significant ischemia at <2 metabolic equivalents (METs) of activity [32].

The two essential components of CR are (1) supervised exercise training and (2) disease specific self-care training and counseling. While techniques may vary, emerging therapies are providing significant morbidity and mortality improvements for patients with HF. Patients are encouraged to begin supervised exercise training to a goal of 3–7 METs per week for a target of >30 min per session 4 days/week. Supervised exercise training in this patient class should be viewed as effective and safe.

Transitions of Care

Transitions of care are a key area of vulnerability for HF patients. For many, hospitalizations are the result of a progressive decline in function. In this population, complex and multidrug medical regimens change frequently and are often changed during or as a result of hospitalizations. Additional comorbid conditions may also develop necessitating therapy change. Patient education, via clear and concise discharge materials, close outpatient follow-up and instructions on when to seek

medical help are critical to the successful discharge of a HF patient. Early outpatient follow-up within 7–14 days of discharge with a telephone follow-up within 3 days is recommended by the ACC/AHA.

Readmission

Risk factors for readmission include frailty, multiple comorbidities, poor social support, serial readmissions, inappropriate self-care, non-optimized GDMT, among others. Multiple effective strategies to avoid readmission have been studied. The most successful programs are multiphase and include identification of at-risk patients, adequate symptom management, enrolment in CR when appropriate, standardized patient discharge education, re-enforcement of self-care, management of comorbid conditions, as well as early and consistent follow-up. Several clinical risk-prediction tools may be helpful to identify high-risk readmission patients; however, this is an area of continued research. Prior to discharge, providers should attempt to address any barriers to outpatient care such as financial or social support limitations. At each hospitalization and clinic visit, all HF patients should receive reinforcement of HF education including self-care, emergency plans and medical therapy adherence. Providers should identify, utilize, and seek to fortify available resources and outpatient follow-up structures within their own health systems.

When to Refer to Specialists

Advanced Coronary Artery Disease

Evaluation for coronary artery revascularization, through percutaneous intervention (PCI) or coronary artery bypass grafting (CABG) is recommended for all HF patients on GDMT with persistent angina. CABG may be considered in patients with significant LV dysfunction (35–50%) and multivessel CAD when viable myocardium is present. In the setting of severe LV dysfunction (EF <35%) CABG may be considered regardless of myocardium viability, although this is a low grade level of evidence [6].

Valve Diseases

Surgical valve replacement is recommended for all patients with critical aortic stenosis (AS). In the setting of AS, if the predicted surgical mortality is >10%, patients should be considered for transcatheter aortic valve replacement (TAVR) when appropriate. Current studies are underway to compare the efficacy of TAVR in low

surgical risk populations. For patients with mitral valve dysfunction leading to HF, transcatheter mitral valve replacement remains of uncertain benefit; however, procedures such as mitral valve repair or clipping may provide benefit to appropriately selected patients [33].

Atrial Fibrillation

Atrial fibrillation (AF) is a common comorbidity in the setting of HF. Not only is AF an independent risk factor for the development of HF, but its prevalence is directly related to NYHA class irrespective of EF. AF with rapid ventricular response is a potentially reversible cause of HF. For those patients with AF causing HF, treatment should focus on rhythm control [6]. In patients with comorbid AF, either rate or rhythm control may be attempted [34].

Common practice involves initiation of anticoagulation and rate control. Beta-adrenergic blockers are the preferred pharmacologic agents for rate control due to the previously mentioned morbidity and mortality benefits. Should these initial therapies prove ineffective, additional antiarrhythmic drug therapy may be considered. Typical treatment plans will involve initiation of amiodarone and adequate anticoagulation (typically 4 weeks) with interval cardioversion and long-term antiarrhythmic therapy as necessary. If symptoms persist, patients may be referred for AF ablation. Of note, catheter ablation therapy has been shown to be effective but is less likely to remain effective as the disease state progresses due to cardiac remodeling.

Sudden Cardiac Death Prevention and Continuous Resynchronization Therapy

HF, especially from DCM, is often accompanied by significant ventricular remodeling and enlargement. Progression of disease often also involves QRS prolongation and corresponding increase in arrhythmias and incidence of ventricular tachycardia. In selected patients, referral to electrophysiology specialists for implantable cardiac defibrillator placement or continuous resynchronization therapy may be helpful to reduce total mortality and improve symptomatology [35]. Below, is a generalized discussion of indications for implantable cardiac defibrillator placement (ICD) and/or continuous resynchronization therapy (CRT).

ICDs are used for primary and secondary prevention of sudden cardiac death. If patients meet criteria, they should be referred to electrophysiology for ICD placement. While multiple inclusion criteria exist, the ACCF/AHA guidelines state that an ICD is indicated for patients with non-ischemic DCM or ischemic heart disease who are at least 40 days post-MI with HF (NYHA class II or III symptoms), on chronic GDMT if they have LVEF of 35% or less.

Similarly, per the ACCF/AHA guidelines, CRT is indicated for HF patients with LVEF of 35% or less if they are in sinus rhythm, have a left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and are on GDMT with NYHA class II or III symptoms.

Advanced HF

Patients with stage IV symptoms that are refractory to therapy are considered class D or advanced HF. Advanced HF carries a dismal prognosis, with 6-month mortality approaching 75% despite optimal medical therapy [36]. Recent advances have enabled patients with significantly reduced cardiac function to live longer and have a better quality of life, but it is important to refer patients to advanced HF specialists while these treatments are still available to them. Before referring to advanced heart failure specialists, all reversible causes of HF should identified and treated. To maximize the benefit of the referral, patients should be optimized on maximally tolerated GDMT [37]. For those patients with class D HF, providers may choose to involve palliative care early in the medical process to help facilitate goals of care and advanced directives [38].

Conclusions

With the increasing incidence and prevalence of HF, hospitalists may be the first to diagnose HF particularly for new onset HF and in those older than 65. Important symptomatology of HF includes shortness of breath, orthopnea, palpitations, leg edema, and exercise intolerance. Notably, many first presentations of HF occur in the post ACS period. For the initial diagnosis and subsequent presentations of HF exacerbation, pertinent clinical assessment, laboratory and imaging diagnostic testing may be helpful in uncovering the etiology of HF. Treatment of acute HF and management of chronic HF is based on EF and comorbidities influence medication choices. Patient education, symptom management, and supportive therapies help to reduce or limit readmissions. Early referral to advanced specialists, when indicated, enables providers to reduce morbidity and mortality. Providers should encourage open communication and set clear and reasonable expectations for patients as to prognosis and potential benefit from available therapies.

Summary Recommendations

1. Classic symptomatology of CHF includes SOB, DOE, orthopnea, palpitations, leg edema, and exercise intolerance.
2. Initial evaluation of new onset HF should seek to identify possible precipitants that are specific to the patient as this will guide future therapy.

3. HF evaluation includes EKG, assessment of EF and biomarkers, as well as potential metabolic and electrolyte disturbances.
4. Management of HF involves targeted treatment of precipitating conditions, as well as optimization of blood pressure management, coronary perfusion, and inhibition of disordered remodeling.
5. Enrollment in transitional clinics and advanced monitoring are beneficial in preventing hospital readmission.
6. Early referral to advanced specialists (such as Electrophysiology and Advanced Heart Failure) can improve treatment options and survival.
7. In advanced HF, goals of care should be discussed early in therapy and readdressed frequently to align provider–patient expectations.

References

1. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG, American Heart Association Advocacy Coordinating Committee, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology; Council on Epidemiology and Prevention, Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6:606–19. doi:10.1161/HHF.0b013e318291329a.
2. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. JAMA. 2011;306:1669–78. doi:10.1001/jama.2011.1474.
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics—2016 update. Circulation. 2015;CIR.0000000000000350, published online before print 16 Dec 2015.
4. National Center for Health Statistics. Mortality multiple cause micro-data files, 2013: public-use data file and documentation: NHLBI tabulations. http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm#Mortality_Multiple. Accessed 19 May 2015.
5. Incidence and prevalence: 2006 chart book on cardiovascular and lung diseases. Bethesda, MD: National Heart, Lung, and Blood Institute; 2006.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2013;62(16):e147–239. doi:10.1016/j.jacc.2013.05.019.
7. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circulation. 2007;115:1563–70.
8. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001;161:996–1002.
9. Bonow RO, Bennett S, Casey DE, et al. ACC/AHA clinical performance measures for adults with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on performance measures (writing committee to develop heart failure clinical performance measures). J Am Coll Cardiol. 2005;46:1144–78.

10. Halkar M, Wilson Tang WH. Incorporating common biomarkers into the clinical management of heart failure. Curr Heart Fail Rep. 2013;10(4):450–7. doi:10.1007/s11897-013-0165-5.
11. Porapakkham P, Porapakkham P, Zimmet H, et al. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. Arch Intern Med. 2010;170:507–14.
12. Peacock WFIV, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. N Engl J Med. 2008;358:2117–26.
13. Sato Y, Yamada T, Taniguchi R, et al. Persistently increased serum concentrations of cardiac troponin t in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation. 2001;103:369–74.
14. Shah RV, Januzzi JL Jr. Soluble ST2 and galectin-3 in heart failure. Clin Lab Med. 2014;34(1):87–97, vi-vii. doi: 10.1016/j.cll.2013.11.009.
15. Bayes-Genis A, de Antonio M, Vila J, et al. Head-to-head comparison of 2 myocardial fibrosis biomarkers for long-term heart failure risk stratification: ST2 versus galectin-3. J Am Coll Cardiol. 2014;63(2):158–66. doi:10.1016/j.jacc.2013.07.087.
16. Tang WH, Shrestha K, Shao Z, et al. Usefulness of plasma galectin-3 levels in systolic heart failure to predict renal insufficiency and survival. Am J Cardiol. 2011;108:385–90.
17. Mallick A, Januzzi JL Jr. Biomarkers in acute heart failure. Rev Esp Cardiol (Engl Ed). 2015;68(6):514–25.
18. Expert Group on Biomarkers. Biomarkers in cardiology—Part 1—in heart failure and specific cardiomyopathies. Arq Bras Cardiol. 2014;103(6):451–9.
19. Cosse C, Sabbagh C, Kamel S, Galmiche A, Regimbeau J-M. Procalcitonin and intestinal ischemia: a review of the literature. World J Gastroenterol. 2014;20(47):17773–8. doi:10.3748/wjg.v20.i47.17773.
20. Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens. 2004;13(2):163–70.
21. Valle-Munoz A, Estornell-Erill J, Soriano-Navarro CJ, et al. Late gadolinium enhancement-cardiovascular magnetic resonance identifies coronary artery disease as the aetiology of left ventricular dysfunction in acute new-onset congestive heart failure. Eur J Echocardiogr. 2009;10:968–74.
22. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. J Am Coll Cardiol. 2009;53:530–53.
23. van den Broek SA, van Veldhuisen DJ, de Graeff PA, Landsman ML, Hillege H, Lie KI. Comparison between New York Heart Association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1992;70(3):359–63.
24. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure: Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med. 1996;335:1107–14.
25. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004. doi:10.1056/NEJMoa1409077.
26. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C, 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. J Am Coll Cardiol. 2016, doi:10.1016/j.jacc.2016.05.011.

27. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709–17.
28. Thadani U, Jacob RG. Isosorbide dinitrate/hydralazine: its role in the treatment of heart failure. Drugs Today (Barc). 2008;44(12):925–37. doi:10.1358/dot.2008.44.12.1131826.
29. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336:525–33.
30. Currie GM, Wheat JM, Kiat H. Pharmacokinetic considerations for digoxin in older people. Open Cardiovasc Med J. 2011;5:130–5. doi:10.2174/1874192401105010130.
31. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
32. Ades PA, Keteyian SJ, Balady GJ, Houston-Miller N, Kitzman DW, Mancini DM, Rich MW. Cardiac rehabilitation exercise and self-care for chronic heart failure. JACC Heart Fail. 2013;1(6):540–7.
33. Wan B, Rahnavardi M, Tian DH, et al. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. Ann Cardiothorac Surg. 2013;2(6):683–92. doi:10.3978/j.issn.2225-319X.2013.11.02.
34. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358:2667–77.
35. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:1329–38.
36. Hershberger RE, Nauman D, Walker TL, et al. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory end-stage heart failure. J Card Fail. 2003;9:180–7.
37. Fanaroff AC, DeVore AD, Mentz RJ, Daneshmand MA, Patel CB. Patient selection for advanced heart failure therapy referral. Crit Pathw Cardiol. 2014;13(1):1–5. doi:10.1097/HPC.0000000000000004.
38. Fendler TJ, Swetz KM, Allen LA. Team-based palliative and end-of-life care for heart failure. Heart Fail Clin. 2015;11(3):479–98. doi:10.1016/j.hfc.2015.03.010.

Chapter 2
Hospital Management of Migraine

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Emergent Headache

While headaches are common and often benign medical conditions, it is important to be aware of and rule out emergent or malignant presentations of headache. For example, acute onset headaches described as the "worst headache of my life" warrant urgent diagnostic imaging to rule out the possibility of subarachnoid hemorrhage [1].

While acute headaches are worrisome, progressive headaches with focal deficits, neurocognitive deficits, or seizures are also concerning, as they can be signs of increased intracranial pressure, indicating more serious pathologies. Emergent headaches are also seen in presentations of ischemic and hemorrhagic stroke, infectious etiologies concerning for meningitis or encephalitis, and as a sequela of substance abuse. These emergencies may require initial evaluation with a non-contrast CT [2]. Further evaluation with appropriate diagnostic modalities will be dependent on working differential diagnoses at the time for possible etiology of headache. For a comprehensive list of differential diagnosis for emergent life-threatening headache, refer to Table 2.1.

Once appropriate workup has been completed and a diagnosis of primary headache has been established attention can be paid to reduction and amelioration of headache (Table 2.2).

Migraines account for one of the most common causes of primary headache and affect approximately 12% of the population [3]. Typically, management of acute migraine is addressed in an outpatient setting. Occasionally migraine headaches are

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Table 2.1 Emergent or life-threatening headache etiologies

Subarachnoid hemorrhage
Rupture of intracranial aneurysm
Carotid and vertebral artery dissections
Hemorrhagic and ischemic infarcts
Pituitary apoplexy
Venous sinus thrombosis
Temporal arteritis
Acute glaucoma
Pre-eclampsia
Hypertensive encephalopathy (PRES)
Cerebellar infarction
Meningitis
Encephalitis
Intracranial lesions/masses
Idiopathic

Table 2.2 ICHD-3 classification of headaches

Migraine
Migraine without aura
Migraine with aura
Chronic migraine
Probable migraine
Episodic syndromes that may be associated with migraine
Tension type headache
Infrequent episodic tension-type headache
Frequent episodic tension-type headache
Chronic tension-type headache
Probable tension-type headache
Trigeminal autonomic cephalalgias (TACs)
Cluster headache
Paroxysmal hemicrania
Short-lasting unilateral neuralgiform headache attacks
Hemicrania continua
Probable trigeminal autonomic cephalalgia
Other primary headache disorders
Primary cough headache
Primary exercise headache
Primary headache associated with sexual activity
Primary thunderclap headache
Cold-stimulus headache
External-pressure headache
Primary stabbing headache
Nummular headache

(continued)

Table 2.2 (continued)

Hypnic headache
New daily persistent headache (NDPH)
Headache attributed to trauma or injury to the head and/or neck
Acute headache attributed to traumatic injury to the head
Persistent headache attributed to traumatic injury to the head
Acute headache attributed to whiplash
Acute headache attributed to craniotomy
Persistent headache attributed to craniotomy
Headache attributed to cranial or cervical vascular disorder
Headache attributed to ischemic stroke or transient ischemic attack
Headache attributed to non-traumatic intracranial hemorrhage
Headache attributed to unruptured vascular malformation
Headache attributed to arteritits
Headache attributed to cervical carotid or vertebral artery disorder
Headache attributed to cerebral venous thrombosis
Headache attributed to other acute intracranial arterial disorder
Headache attributed to genetic vasculopathy
Headache attributed to pituitary apoplexy
Headache attributed to non-vascular intracranial disorder
Headache attributed to increased cerebrospinal fluid pressure
Headache attributed to low cerebrospinal fluid pressure
Headache attributed to non-infectious inflammatory disease
Headache attributed to intracranial neoplasia
Headache attributed to intrathecal injection
Headache attributed to epileptic seizure
Headache attributed to chiari malformation type 1
Headache attributed to other non-vascular intracranial disorder
Headache attributed to a substance or its withdrawal
Headache attributed to use of or exposure to a substance
Medication-overuse headache
Headache attributed to substance withdrawal
Headache attributed to infection
Headache attributed to intracranial infection
Headache attributed to systemic infection
Headache attributed to disorder of homeostasis
Headache attributed to hypoxia and/or hypercapnia
Dialysis headache
Headache attributed to arterial hypertension
Headache attributed to hypothyroidism
Headache attributed to fasting
Cardiac cephalalgia
Headache attributed to other disorder of homeostasis

(continued)

Table 2.2 (continued)

Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or facial or cervical structure
Headache attributed to disorder of cranial bone
Headache attributed to disorder of the neck
Headache attributed to disorder of the eyes
Headache attributed to disorder of the ears
Headache attributed to disorder of the nose or paranasal sinuses
Headache attributed to disorder of the teeth or jaw
Headache attributed to temporomandibular disorder (TMD)
Head or facial pain attributed to inflammation of the stylohyoid ligament
Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
Headache attributed to psychiatric disorder
Headache attributed to somatization disorder
Headache attributed to psychotic disorder
Painful cranial neuropathies and other facial pain
Trigeminal neuralgia
Glossopharyngeal neuralgia
Nervus intermedius (facial nerve) neuralgia
Occipital neuralgia
Optic neuritis
Headache attributed to ischemic ocular motor nerve palsy
Tolosa-hunt syndrome
Paratrigeminal oculosympathetic (Raeder's) syndrome
Recurrent painful ophthalmoplegic neuropathy
Burning mouth syndrome (BMS)
Persistent idiopathic facial pain (PIFP)
Central neuropathic pain
Other headache disorders
Headache not elsewhere classified
Headache unspecified

severely debilitating requiring inpatient hospital management [4]. A European study determined that the cost to society for management of headaches far outweighed the costs of many other neurologic disorders including stroke, multiple sclerosis, and Parkinson's disease [5]. This study emphasizes the profound impact of migraine headaches, and reinforces the need for physicians to have an in-depth understanding of migraine and its treatment.

Migraine as a Spectrum of Disease

Diagnosis of migraine is made based on criteria provided by International Headache Society (IHS) classification [6]. Migraines are classified by two subtypes: migraine with and without aura. Migraine without aura is a clinical syndrome characterized by

Table 2.3 ICHD criteria for migraine without aura—obtained from www.ichd-3.org

Diagnostic criteria:
A. At least five attacks [1] fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated) [2, 3]
C. Headache has at least two of the following four characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Table 2.4 ICHD criteria for migraine with aura—obtained from www.ichd-3.org

Diagnostic criteria:
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal
C. At least two of the following four characteristics:
1. At least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession
2. Each individual aura symptom lasts 5–60 min [1]
3. At least one aura symptom is unilateral [2]
4. The aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

a headache with associated features described in the International Classification of Headache Disorders (ICHD) criteria (refer to Table 2.3). Migraine with aura is further subdivided into aura without headache, migraine with brainstem aura, hemiplegic migraine, and retinal migraine. Migraine with typical aura (Table 2.4) is characterized by transient focal neurologic symptoms that can either precede or accompany the headache (Table 2.5). Patients can have premonitory symptoms that occur hours to days prior to onset of the headache and knowledge that these symptoms are part of the clinical syndrome of migraines is important. Symptoms can include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue, and neck stiffness and/or pain. Chronic migraines (Table 2.6), on the other hand, are defined as headaches that occur 15 or more days per month, for >3 months; for 8 of those days per month, headaches must meet migraine criteria. Preventive migraine treatments are used on an outpatient basis with the goal of decreasing headache frequency [6].

Table 2.5 ICHD criteria for migraine with brainstem aura—obtained from www.ichd-3.org

Diagnostic criteria:
A. At least two attacks fulfilling criteria B–D
B. Aura consisting of visual, sensory, and/or speech/language symptoms, each fully reversible, but no motor [1] or retinal symptoms
C. At least two of the following brainstem symptoms:
1. Dysarthria
2. Vertigo
3. Tinnitus
4. Hypacusis
5. Diplopia
6. Ataxia
7. Decreased level of consciousness
D. At least two of the following four characteristics:
1. At least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession
2. Each individual aura symptom lasts 5–60 min [2]
3. At least one aura symptom is unilateral [3]
4. The aura is accompanied, or followed within 60 min, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

Table 2.6 ICHD criteria for chronic migraine—obtained from www.ichd-3.org

Diagnostic criteria:
A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months [2] and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria Band C for 1.2 Migraine with aura
C. On ≥8 days per month for >3 months, fulfilling any of the following [3]:
1. Criteria C and D for 1.1 Migraine without aura
2. Criteria B and C for 1.2 Migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

Rationale Behind Acute Treatment of Migraine

Acute treatment of primary migraines (headache episodes with no underlying organic pathologies) aims to relieve the symptoms of pain, photophobia, phonophobia, and nausea [7]. Untreated migraines can lead to complications which include status migrainosus (migraine lasting >72 h), persistent aura, migraine infarction, and seizures [6]. Sub-optimal treatment of acute migraines is also a known risk factor that predisposes patients to development of chronic migraines. The goal of neurologists and headache specialists in migraine management is to adequately control

migraines in the outpatient setting and reduce Emergency Department (ED) visits. Combination analgesics with nonsteroidal anti-inflammatory agents (NSAIDs) and triptans remain the first line of abortive treatment unless the patient has contraindications for either class of drugs. Typically, by the time of presentation to the ED, patients are likely to have tried abortive treatment and rescue therapies without adequate relief.

Goals of Inpatient and ED Management of Acute Migraine

Setting migraine treatment goals at the start of the hospitalization period will help create realistic patient expectations. While chronic headache and migraine may be incapacitating, it is important to focus on headache reduction as opposed to elimination. Patients should be advised that a realistic goal of treatment is to reduce the frequency and severity of their presenting migraine symptoms and migraine-related disability and not complete remission. If the decision to start a prophylactic medication as an inpatient is made, patients should be informed of the expected interval between starting a new medication and when relief of symptoms is likely to occur. Once the target dose of medication is reached, six to eight weeks of treatment might be needed before maximum benefits are realized [8]. This knowledge can help improve adherence and reduce patient frustration.

Finally, it is important to identify any psychosocial stressors and/or potential gain for the patient from hospitalization. Chronic migraine is often accompanied by comorbidities such as sleep disorders, fatigue, other pain disorders, other neurologic disorders, psychiatric illness, cerebrovascular disease, cardiovascular disease, and gastrointestinal problems [8]. Identifying and addressing these comorbidities are key to successful acute and chronic management of migraines.

Headache Therapies in the Emergency Department (ED)

General principles of treating migraine in the ED include adequate hydration with intravenous fluids unless contraindicated, treatment of headache with non-opioid medications, use of IV medications in attempts to provide rapid relief, and, as mentioned above, establish realistic expectation for goals of treatment [4]. Prior to initiation of treatment, several factors should be considered. The patient's comorbid conditions, past response to treatment, current medication list, and medications tried for migraine treatment prior to arrival must be evaluated. For example, exercise caution when considering using triptans in patients with cardiovascular risk factors, NSAIDs in those with history of GI bleed, and dopamine receptor antagonists in hypotensive patients. Drug–drug interactions also need to be

reviewed. For example, concurrent use of topamax and valproic acid increases risk of hyperammonemia while use of DHE within 24 h of a triptan can increase risk of vasospasm [4]. While polypharmacy should be used cautiously, combination therapy is utilized to manage intractable headache as medications with different mechanisms of action have been found to produce a synergistic effect. Based on current theories of migraine pathophysiology, the goal of treatment is to block glutamate effect, enhance and increase GABA and serotonin concentrations, decrease dopamine and histamine effects and CNS inflammation [4]. A systematic review by the Canadian Headache Society in 2015 of acute migraine treatment in the ED strongly recommended four treatments for headache management in the ED: metoclopramide, prochlorperazine, ketorolac, and sumatriptan [9]. A subsequent assessment by the American Headache Association (AHA) in 2016 of parenteral pharmacotherapies in acute treatment of migraines based on available evidence listed dexamethasone, prochlorperazine, sumatriptan, and metoclopramide as drugs that should be administered in the ED unless contraindicated (Class A recommendation). In the study, dexamethasone was recommended based on evidence that it helped in prevention of migraine in patients discharged from the ED, not for treatment of acute management. Other medications that can be considered for usage included acetaminophen, acetylsalicylic acid, chlorpromazine, dipyrone, droperidol, diclofenac, dexketoprofen, haloperidol, ketorolac, and valproic acid (Class B recommendation). Medications to be avoided in acute migraines included diphenhydramine, hydromorphone, lidocaine, morphine, and octreotide (Table 2.7) [10].

Some commonly used medications and doses utilized in the ED are listed in Table 2.8. If these agents have not been attempted as abortive therapies for migraines and are not contraindicated, they may be considered in treatment of these refractory headaches. If there are signs of focal neurological deficit concurrent with migraines, it would be prudent to avoid triptan therapy as this can actually precipitate ischemia in certain patient populations.

Table 2.7 Proposed headache protocol

2 g IV Magnesium Sulfate BID
1 g IV Depacon BID
1 g IV Solumedrol BID (as appropriate)

Table 2.8 Acute treatment for migraine in the emergency room

Hydration
Depacon 5–10 mg/kg IV rate <20 mg/min
IV Anti-emetics
- Prochlorperazine (Compazine)
- Metoclopramide (Reglan)
- Promethazine (Phenergan)
Steroids
- Methylprednisolone (Solumedrol) 1 g IV once
- Prednisone taper

Proposed IV Treatment of Acute Inpatient Headache

Table 2.7 shows a proposed combination of IV medications that can be used safely in a majority of patient populations. This treatment has been used successfully in clinical settings in a variety of headache subtypes and patient populations, including immune-suppressed patients and patients with liver and kidney injury. While 3 days of treatment did not completely eliminate the headache, headache severity was reduced to a tolerable level, at which point, patients can be discharged from the hospital and focus on outpatient management.

Magnesium Sulfate

A link between magnesium deficiency and migraine has been identified in multiple studies suggesting different mechanisms of action based on our understanding of migraine pathophysiology. Magnesium sulfate may exert a therapeutic effect through its antagonism of *N*-methyl-D-aspartate (NMDA) receptor, and/or its blockade of cortical spreading depression [4]. Patients suffering from migraines tend to release elevated levels of magnesium, possibly due to high stress levels, resulting in a state of serum hypomagnesemia. Similarly, low magnesium levels are associated with lower levels of neurotransmitter release, platelet aggregation, and vasoconstriction, all features that have an established association with migraines [11]. Conflicting evidence exists regarding the efficacy of magnesium sulfate infusion in the treatment of patients with migraine. Mauskop et al. studied the short-term and long-term effects of IV magnesium sulfate infusion and found that 86% of patients with low serum magnesium levels had effective pain relief [12, 13]. Other studies comparing magnesium sulfate to placebo did not show significant difference.

Magnesium sulfate administration for the treatment of migraine currently remains an off-label use of the medication. While there is no consensus on the dosage required for treatment of migraine, a dose of 1 g is commonly adopted in many study protocols [12]. Magnesium sulfate use is contraindicated in patients with severe renal failure and has been associated with pain at the injection site and warm flushes [14]. In patients without severe renal failure, it has been our clinical experience that Magnesium Sulfate 2 g IV twice daily is well tolerated and can reduce headache in conjunction with the other parts of the proposed acute migraine therapy.

Depacon (Valproate Sodium Injection)

Depacon is a valuable medication that shows potential for treatment of acute headache. While the oral form divalproex is used as a prophylactic treatment for migraine, recent studies provide evidence that a single dose of the IV form

Depacon provided symptomatic relief in 73% of patients tested [15, 16]. The mechanism of action of the drug is largely unknown; however, its ability to suppress neurogenic inflammation via increased gamma-aminobutyric acid (GABA) levels in the brain represents a possible explanation in the suppression of headache [16]. It should be particularly considered when dihydroergotamine drugs are ineffective or contraindicated. Similar to usage of magnesium in treatment of eclampsia, it is an anticonvulsant, and thus, an off-label medication for the treatment of migraine.

One randomized control trial showed that valproate and dexamethasone were both effective in treating headache. Valproate was found to be helpful in treating patients with aura [17]. Another study showed that valproic acid treatment resulted in fewer frequent headaches and also decreased pain intensity [18]. As mentioned above, valproate was listed as a possibly effective medication by AHS with few adverse effects that may be offered in acute presentation of headache [10].

The dosing protocol of Depacon for adults initially includes optimizing the dose, between 1-2 g/day [14]. Our proposed dose based on clinical experience and patient response is 1 g IV twice daily. The medication is contraindicated in patients with a history of hepatitis or hepatic disease. Side effects include pancreatitis, extrapyramidal symptoms, cognitive disorders and behavioral disturbances, confusion, severe allergic reactions (Lyell's and Stevens-Johnson syndromes), amenorrhea, thrombocytopenia, and prolongation of bleeding time [14]. There is also a risk of neural tube defects, limb malformations, and craniofacial abnormalities if used during the first trimester of pregnancy [14].

Corticosteroids

IV corticosteroids is a common adjunct in treatment of acute migraines. There are studies to suggest that dexamethasone may not be as effective in acute management of migraines in the ED; however, a meta-analysis of 25 studies showed potential benefit in using IV dexamethasone to prevent early headache recurrence for up to 72 h after ED discharge [10, 19]. In the meta-analysis, dexamethasone dose ranging from 8 to 24 mg was used. In the author's experience, methylprednisolone at a dose of 1g IV BID is adequate. Steroids are not recommended in patients with active peptic ulcer disease and poorly controlled infections. Adverse effects of these medications include adrenal suppression, muscle atrophy, growth retardation, increased susceptibility to infections, hypokalemia, sodium and water retention, and osteoporosis [14]. Due to this consideration, it is recommended that the duration of IV steroid use not exceed 5–7 days, and to review diagnostic modalities if there is no response to usage after 3 days, as there may be more insidious etiology of the headache involved.

Adjuvant Therapies

Antiemetics are commonly used as adjunctive therapy for treatment of migraine and associated symptoms. Metoclopramide has the strongest evidence for efficacy in migraines. While metoclopramide usages do come with risk of extrapyramidal side symptoms (EPS) and QTc prolongation, these side effects are uncommon with intermittent oral dosing used to treat migraine attacks. For refractory patients, prochlorperazine may also be used but does have an increased risk of developing EPS when compared to metoclopramide [20].

Diphenhydramine is another medication commonly used in the inpatient setting for management of headache pain. A randomized, double-blind, clinical trial compared metoclopramide and diphenhydramine versus metoclopramide and reglan for treatment of acute migraine in an ED along with IV diphenhydramine when administered as adjuvant therapy in this trial. This did not improve migraine outcomes and the rates of adverse effects, including extrapyramidal symptoms such as akathisia, were comparable between the groups [21]. For this reason, this treatment is not recommended by AHS in the management of acute migraine [10].

Anxiolytics also may have a role in migraine treatment. A 2015 meta-analysis study showed that amitriptyline was more likely than placebo to produce a 50% reduction in episodic migraine headaches. The average rate of withdrawals was 37% (range 20–52%). Another trial, however, found amitriptyline ineffective in treating chronic daily headaches.

Six SSRI and one SNRI placebo controlled trials were reviewed for this chapter. Five of the trials focused on migraines and one on chronic daily headaches. For treatment of migraine headaches, two SSRIs (femoxitine and sertraline) were no more effective than placebo, while fluoxetine was effective at 12 weeks. A single trial of venlafaxine did show some benefit at 8 weeks. For chronic daily headache, one trial found that there was no relief benefit when using fluoxetine. Only one trial showed the ability of fluoxetine to reduce headaches by at least 50%, however, this trial found no benefit over placebo [22].

Pitfalls in Headache Management

Opioids are commonly used in the acute setting for management of headaches. The American Headache Society discourages the use of opioids as first line therapy for management of migraines. Evidence shows that IV opioids are associated with increased ED visits, dependence, and progression of migraine disorder [10]. Hydromorphone metabolites, the phenanthrene, methadone, and piperidine classes (including morphine and derivatives, such as oxycodone hydromorphone

and hydrocodone, but excluding oxymorphone) have been linked to opioid induced hyperalgesia (OIH), a state where prolonged opioid use leads to a decreased pain threshold [23]. In the case of morphine, its glucoronide metabolite is associated with a neuro-excitatory effect and results in the OIH [24]. Not only is use of opioids associated with OIH, but one study also found that opioid use in episodic migraine doubled a person's chance of developing chronic migraine [25].

As part of management considerations, it is important to evaluate medication overuse headache (MOH) in patients. The International Headache Society defines MOH as headaches occurring greater than 15 days per month and use of at least one medication for greater than 3 months with the intention of relieving the headache [6]. One US case control study found that 32% of chronic headaches were classified as medication overuse headaches [26]. Current treatment for MOH involves withdrawal of medication, a process often requiring hospitalization [24]. An important aspect of MOH to consider is opioid overuse headache. The international headache society defines this as a headache associated with intake of at least one opioid on more than 10 days per month for 3 months [6]. In addition to opioids, overuse of abortive medication, including acetaminophen, nonsteroidal anti-inflammatory drugs, triptans, butalbital, caffeine, and narcotics, is found in two-thirds of chronic daily headache patients and it has been suggested that clinicians set limits on the use of abortive migraine drugs [8, 27].

Conclusion

Headaches can be a common symptom of multiple systemic and intracranial pathologies, and it is critical to rule out neurologic emergencies prior to treatment of headache. Migraines are the most common primary headache disorder and intractable migraines can be difficult to manage. Some key aspects to optimizing chances for successful management of migraines include setting up realistic expectations of treatment which in the inpatient setting should be decreasing pain intensity to a tolerable state for the patient and not necessarily being headache free. If a certain case of intractable headache is identified to be secondary to medication overuse, then detoxification in a controlled setting might be necessary. Ensuring that the patient is made aware of appropriate use of abortive medications is imperative. Furthermore, after a patient is diagnosed with chronic migraines, the clinician should initiate prophylactic medication as well as educate the patient on the importance of adherence. Finally, identification of comorbid conditions and migraine triggers should be identified so that it can be properly addressed either as an inpatient or with outpatient follow-up on discharge. These measures should aid in the prevention and treatment of migraine headaches, and should improve patient discomfort.

References

1. Gould L, Petrovic R, O'Donnell MJ, Silva J, Lindsay MP, Fang J, et al. Association between time-to-presentation and clinical outcome in patients with subarachnoid hemorrhage: an observational study. Can J Neurosci Nurs. 2011;33(3):33–7.
2. Levin M. Approach to the workup and management of headache in the emergency department and inpatient settings. Semin Neurol. 2015;35(6):667–74.
3. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and need for preventive therapy. Neurology. 2007;68(5):343–9.
4. Rozen T. Emergency department and inpatient management of status migrainosus and intractable headache. Continuum. 2015;21(4):1004–17.
5. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. Eur J Neurol. 2005;12(Suppl 1):1–27.
6. Headache Classification Committee of the International Headache Society (IHS). Headache Classification Committee of the International Headache Society (IHS), 3rd edition (beta version). Cephalalgia. 2013;33:629–808.
7. Freitag FG, Schloemer F. Medical management of adult headache. Otolaryngol Clin N Am. 2014;47(2):221–37.
8. Schwedt TJ. Chronic migraine. BMJ. 2014;348:g1416.
9. Orr SL, Aube M, Becker WJ, et al. Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. Cephalalgia. 2015;35(3):271–84.
10. Orr S, Friedman B, Christie S, Minen M, Bamford C, Kelley N, Tepper D. Management of adults with acute migraine in the emergency department: the American headache society evidence assessment of parenteral pharmacotherapies. Headache. 2016;56(6):911–40.
11. Choi H, Parmar N. The use of intravenous magnesium sulphate for acute migraine: meta-analysis of randomized controlled trials. Eur J Emerg Med. 2014;21(1):2–9.
12. Mauskop A, Altura BT, Cracco RQ, Altura BM. Intravenous magnesium sulfate rapidly alleviates headaches of various types. Headache. 1996;36(3):154–60.
13. Demirkaya S, Vural O, Dora B, Topcuoglu MA. Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. Headache. 2001;41(2):171–7.
14. World Health Organization. Model list of essential drugs. 18th ed. 2013. http://www.who.int/medicines/publications/essentialmedicines/en/. Updated October 2013. Accessed Sept 2016.
15. Mathew NT, Kailasam J, Meadors L, Chernyschev O, Gentry P. Intravenous valproate sodium (depacon) aborts migraine rapidly: a preliminary report. Headache. 2000;40(9):720–3.
16. Schwartz TH, Karpitskiy VV, Sohn RS. Intravenous valproate sodium in the treatment of daily headache. Headache. 2002;42(6):519–22.
17. Mazaheri S, Poorolajal J, Hosseinzadeh A, Fazlian M. Effect of intravenous sodium valproate vs dexamethasone on acute migraine headache: a double blind randomized clinical trial. PLoS One. 2015;10(3):e0120229. doi:10.1371/journal.pone.0120229.
18. Starling A, Vargas B. A narrative review of evidence-based preventative options for chronic migraine. Curr Pain Headache Rep. 2015;19(10):49.
19. Colman I, Friedman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomized controlled trials for preventing recurrence. BMJ. 2008;336(7657):1359–61.
20. Becker WJ. Acute migraine treatment. Continuum. 2015;21(4):953–72.
21. Friedman BW, Cabral L, Adewunmi V, et al. Diphenhydramine as adjuvant therapy for acute migraine: an emergency department-based randomized clinical trial. Ann Emerg Med. 2016;67(1):32–9.
22. Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. PLoS One. 2015;10(7):e0130733. doi:10.1371/journal.pone.0130733.

23. Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145–61.
24. Johnson JL, Hutchinson MR, Williams DB, Rolan P. Medication-overuse headache and opioid-induced hyperalgesia: a review of mechanisms, a neuroimmune hypothesis and a novel approach to treatment. Cephalalgia. 2013;33(1):52–64.
25. Bigal M, Lipton R. Excessive opioid use and the development of chronic migraine. Pain. 2009;142(3):179–82.
26. Westergaard M, Munksgaard S, Bendtsen L, Jensen R. Medication-overuse headache: a perspective review. Ther Adv Drug Saf. 2016;7(4):147–58.
27. Yancey JR, Sheridan R, Koren KG. Chronic daily headache: diagnosis and management. Am Fam Physician. 2014;89(8):642–8.

Chapter 3
Candidemia: New Directions for Management and Treatment

Amanda Theppote

Epidemiology

Candidemia has emerged as an important and common cause of bloodstream infections in hospitals, accounting for the third or fourth most common nosocomial bloodstream infection [1, 2]. The incidence of candidemia has increased over the past decade largely due to prolonged use of broad-spectrum antibiotics, novel immunosuppressive treatments, parenteral nutrition, and increasing elderly population [3]. Although candidemia is often cited to be a common bloodstream infection in intensive care units, candidemia in internal medicine wards is on the rise, with a prevalence rate ranging from 24 to 57% [4]. Other risk factors of candidemia include the presence of central venous catheters, critical illnesses necessitating long-term ICU admission, and abdominal surgery [1, 2]. Common risk factors are summarized in Table 3.1.

Despite treatment with antifungals, mortality rate due to candidemia can be as high as 40% [2]. One study revealed that a delay in antifungal treatment for bloodstream infections of more than 48 h was associated with a greater risk in hospital mortality compared to those who were treated within a 48-h window [4]. In addition to early antifungal treatment, the removal of central venous catheters within 48 h showed survival benefits [3].

Although *Candida albicans* is the most common pathogenic *Candida* species, other non-albicans species have emerged to be significant blood stream infections [5]. *C. parapsilosis* and *C. glabrata* followed by *C. tropicalis* and *C. krusei* are important isolates found in candidemia [6]. Significant geographical differences exist among Candida species where *C. glabrata* isolates were more common in

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Table 3.1 Common risk factors for candidemia

• Broad-spectrum antibiotic use
• Abdominal surgery, with particular risk in patients with anastomotic leakage or multiple laparotomies
• Critically ill patients in long-term intensive care
• Central venous catheters
• Total parental nutrition
• Hemodialysis
• Solid organ transplantation
• Solid organ and hematologic malignancies
• Glucocorticoid use

North America and Northern Europe and *C. parapsilosis* is more prominent in South America, Asia, and Southern Europe [2, 5]. The variation in virulence, with *C. parapsilosis* and *C. krusei* being less virulent than *C. albicans*, *C. glabrata*, and *C. tropicalis*, is an important factor in patient mortality [2, 5].

Candidiasis should be considered as a differential in patients with unexplained fevers, decompensation without a clear etiology, persistent leukocytosis, recent abdominal surgery, and central venous catheters [1].

Diagnosis of Candidemia

Cultures have been the mainstay of diagnosing candidemia; however, other laboratory investigations have become adjuncts to blood cultures. The sensitivity to blood cultures is purported to be around 50% [7]. The limitations of cultures include slow turnaround times, with a median positivity of 2–3 days, and blood cultures may be positive late in the course of the infection [1, 2]. Further, negative cultures can result from deep-seated infections that have cleared the blood stream, intermittent infections, and candidiasis acquired from direct inoculation [1, 8]. Any patients with a positive blood culture should have prompt antifungal therapy. Blood cultures are to be drawn every day or every other day until evidence of candida clearance to establish the duration of antifungal therapy [1]. The duration of treatment has been suggested to be 14 days following documented bloodstream clearance [1].

In addition to blood cultures, candida mannan antigens, antimannan antibodies, and β-D-glucan are also utilized as markers for candidemia. Although antigen detection is rapidly cleared in the bloodstream, one study found that the antigen/antibody test was positive before blood cultures in 73% of patients [9, 10]. However, the combined mannan/antimannan antibody assay is only approved for use in Europe at this time [1].

β-D-glucan test is approved by the FDA and is commonly used as an adjunct to cultures in the United States. β-D-glucan is cell wall constituent of not only *Candida* species, but also found in *Aspergillus* species and *Pneumocystis jiroveci* [1]. Patients with fungal colonization, gram positive and gram negative bacteremia, who received

albumin, immunoglobulins, certain antibiotics (amoxicillin-clavulanate or piperacillin-tazobactam), or patients on hemodialysis, can have false positive β-D-glucan tests [1]. As such, β-D-glucan detection has diagnostic limitations due to its poor specificity and can yield false positive results. The role of β-D-glucan test can be beneficial in targeted patients who are at high risk of invasive candidiasis, response to antifungal therapy, and in populations with intermediate prevalence of Candida as several studies have shown high negative predictive values [5, 11].

Patients with candidemia should receive a dilated funduscopic examination to assess for ocular involvement as patients are at high risk of developing sight-threatening endophthalmitis [12]. Endophthalmitis from candidemia typically affect the posterior chamber of the eye and spread endogenously through the blood. *C. albicans* is the most common species causing endophthalmitis; however, all *Candida* species have been shown to cause the infection [1]. Ophthalmologists should be consulted in all patients with endophthalmitis as surgical intervention may be warranted, such as intravitreal injection of antifungal agents or vitrectomy [1]. It is recommended that treatment be directed towards susceptible isolates. For species susceptible to azoles, fluconazole and voriconazole are recommended as these antifungals have satisfactory concentrations within the eye [1]. For azole-resistant species, liposomal AmB with or without oral flucytosine is recommended [1]. Duration of therapy is typically 4–6 weeks with repeat ophthalmological examinations to assess clearance of infection [1].

Treatment

Antifungal therapy for candidemia consists of three major categories: polyenes, echinocandins, and triazoles.

Polyenes consist of amphotericin B deoxycholate (AmB), liposomal AmB, and AmB lipid complex. Since the 1950s, polyenes were the standard of therapy for candidiasis until the discovery of azoles [13]. Polyenes increase the permeability of cell membrane by producing aqueous pores within the membrane, causing leakage of cytoplasmic material and eventual death of the organism [14]. Amphotericin B deoxycholate has a narrow therapeutic index, with nephrotoxicity as the most common adverse effect [1]. Acute kidney injury and tubular acidosis is seen in up to 50% of patients who receive AmB deoxycholate therapy. [15, 16] Although lipid formulas are less nephrotoxic and have fewer infusion related reactions, they are considerably more expensive than AmB deoxycholate [1, 17]. Data have shown that nephrotoxicity, that is largely irreversible, due to AmB deoxycholate was associated with a higher mortality, length of stay, and cost [18]. This has led to many physicians to use the lipid formulations of AmB in high risk patients [1].

Triazoles, which include itraconazole, fluconazole, voriconazole, and posaconazole, have been an important antifungal since the 1960s [14]. The azoles inhibit cytochrome P450 enzymes and sterol C-14-α-demethylation, resulting in alteration of cell membrane and function thereby arresting fungal growth [14, 19]. Generally,

azoles are well tolerated; however, hepatic toxicity can occur and are commonly associated with higher concentrations of voriconazole [1].

Fluconazole is readily absorbed with a high bioavailability of approximately 90% between oral and intravenous (IV) formulations, with intestinal absorption not limited by gastric pH or food consumption [1]. Voriconazole is available in both oral and IV suspensions. Oral voriconazole is not affected by gastric pH, but its activity is decreased with administration of food [20]. Although oral formulations of voriconazole does not require dosage adjustments in patients with renal insufficiency, intravenous voriconazole is not recommended in hemodialysis patients and patients with a creatinine clearance of <50 ml/min as there is a potential risk of cyclodextrin accumulation and nephrotoxicity [1, 6]. Although itraconazole and posaconazole exhibit activity against *Candida* spp., they are not recommended as primary therapy for candidemia [1].

Echinocandins (such as caspofungin, anidulafungin, and micafungin) are fungicidal against *Candida* spp. by inhibiting 1,3-β-glucan, an integral component of fungal cell wall [14]. They are only available in IV formulations and are well tolerated with minimal adverse effects [6]. Echinocandins do not require dose adjustment in patients on hemodialysis or with renal insufficiency [1]. In patients with moderate hepatic insufficiency (Childs-Pugh 7–9), only caspofungin is recommended to have a dose reduction [1, 21].

New Directions

There has been much debate between azoles (namely fluconazole) and echinocandins as first line therapy for candidemia. Many studies have suggested better outcomes for patients with candidemia treated with echinocandins. In one pooled analysis from seven randomized trials of patient-level data, it revealed that echinocandin therapy was associated with better survival rates and clinical success compared to treatment with triazoles and polyenes in patients infected with *C. albicans* and *C. glabrata* [22]. A multivariate analysis retrospective study showed that early removal of central venous catheters and antifungal treatment with an echinocandin as definitive therapy were associated with higher survival among patients in an internal medicine ward compared to patients treated with fluconazole as definitive therapy [3]. Further, several cohort studies with multivariate analyses revealed better outcomes in patients with catheter removal and echinocandin treatment for candidemia [23, 24].

The increasing data supporting echinocandin therapy and increasing *Candida* strains resistant to fluconazole have shifted guideline recommendations from fluconazole as initial therapy to an echinocandin [1]. However, expert opinion recommends fluconazole as first line therapy in hemodynamically stable patients, who have not previous azole exposure, and patients without risk factors susceptible to *C. glabrata* infection such as diabetes, elderly, or those with underlying malignancy [1]. The Infectious Disease Society of America (IDSA) recommends a step-down

strategy from intravenous echinocandin to oral azole as early as possible once patient becomes clinically stable and blood cultures have cleared [1]. Many studies have reported a minimum of 10 days of parenteral echinocandin therapy prior to a step-down strategy; however a recent study showed similar survival rates and efficacy in an early step-down approach to an oral azole [25]. Although the study was an open label, noncomparative study, it did reveal that an early step-down strategy may shorten the need for intravascular catheters, decrease hospital stay, and may be cost-saving [25].

In association with increasing echinocandin use as first line therapy for candidemia, there is a rise in *Candida* spp. resistance to these antifungals with an incidence of resistance of 2.9–3.1% among *Candida* spp. [26, 27]. Antifungal susceptibility testing may be beneficial in patients failing current antifungal regimen or who have had previous antifungal exposure [27].

Rapid diagnosis for candidemia leads to earlier onset of treatment, which has been shown to reduce patient mortality [28]. Polymerase chain reaction (PCR) assays are relatively new diagnostic tests that can detect *Candida* spp. much quicker than standard culture based investigations. A recent multicenter clinical trial using PCR and T2 magnetic resonance (T2 Candida) revealed to have a 91% sensitivity and 94% specificity in detecting the most common strains of candidemia [28]. Although very promising in rapid detection and identification of *Candida*, standardization of PCR assays and further multicenter validation of assay performance is needed.

Isavuconazole is a newly approved broad-spectrum triazole that is available in both oral and IV formulations. It offers advantages over other azoles by including high bioavailability, expanded spectrum of activity including many fluconazole resistant *Candida*, and has a high prodrug water solubility [29]. A recent phase 3, double-blinded, randomized trial (ACTIVE) comparing IV isavuconazole to an echinocandin (caspofungin) did not meet its primary endpoint of noninferiority in overall treatment [30]. Further post-market surveillance of isavuconazole is needed to further elucidate its safety and efficacy in the treatment of candidiasis.

The diagnosis and treatment of candidemia has changed over the past two decades with new advances in molecular diagnostic tests and the emergence of resistance strains of *Candida*. There has been a shift from azoles to echinocandin as first line therapy with a step-down approach to a triazole, with close consideration of susceptibility and *Candida* species, and patient stability. Early identification and treatment of candidemia improves patient survival.

Key Points

- First line therapy for susceptible isolates is an echinocandin with step-down therapy to azoles typically within 5–7 days for patients who are clinically stable and with negative repeat blood cultures following initiation of therapy.
- Early central venous catheter removal is recommended when source of candidemia is presumed to be from catheter.

- All patients with candidemia should have an ophthalmological exam to assess for endophthalmitis.
- PCR testing in candidemia is a promising new diagnostic test that may shorten time to diagnosis.

References

1. Pappas PG, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of america. Clin Infect Dis. 2016;62(4):e1–50.
2. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med. 2015;373:1445–56.
3. De Rosa FG, et al. The effect on mortality of fluconazole or echinocandins treatment in candidemia in internal medicine wards. PLoS One. 2015;10(5):e0125149. doi:10.1371/journal.pone.0125149.
4. Bassetti M, et al. Candidemia in internal medicine departments: the burden of a rising problem. Clin Microbiol Infect. 2013;19:281–4.
5. Tagliaferri E, Menichetti F. Treatment of invasive candidiasis: between guidelines and daily clinical practice. Expert Rev Anti-Infect Ther. 2015;13(6):685–9.
6. Matthaiou DK, et al. How to treat fungal infection in ICU patients. BMC Infect Dis. 2015;15(205):1–8.
7. Clancy C, Nguyen M. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis. 2013;56:1284–92.
8. Diekema D, et al. The changing epidemiology of healthcare-associated candidemia over three decades. Diagn Microbiol Infect Dis. 2012;73:45–8.
9. Ellepola A, Morrison C. Laboratory diagnosis of invasive candidiasis. J Microbiol. 2005;43:65–84.
10. Year H, et al. Contribution of serological tests and blood culture to the early diagnosis of systemic candidiasis. Eur J Clin Microbiol Infect Dis. 2001;20:864–70.
11. Ostrosky-Zeichner L, et al. Multicenter clinical evaluation of the (1–3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41:654–9.
12. Ruhnke M, et al. Anidulafungin for the treatment of candidaemia/invasive candidiasis in selected critically ill patients. Clin Microbiol Infect. 2012;18:680–7.
13. Sugar A. The polyene macrolide antifungal drugs. In: Peterson PK, Verhoef J, editors. Antimicrobial agent, vol. 1. Amsterdam: Elsevier; 1986. p. 229–44.
14. Ghannoum MA, Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. Clin Microbiol Rev. 1999;12(4):501–17.
15. Girmenia C, et al. Nephrotoxicity of amphotericin B deoxycholate. Clin Infect Dis. 2001;33:915–6.
16. Wingard JR, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergiloosis. Clin Infect Dis. 1999;29:1402–7.
17. Safdar A, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta- analysis. Medicine (Baltimore). 2010;89:236–44.
18. Bates DW, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis. 2001;32:686–93.
19. Zonios D, Bennett J. Update on Azole Antifungals. Semin Respir Crit Care Med. 2008;29(2):198–210. doi:10.1055/s-2008-1063858.
20. Purkins L, et al. Histamine H2-receptor antagonists have no clinically significant effect on the steady-state pharmacokinetics of voriconazole. Br J Clin Pharmacol. 2003;56(Suppl 1):2–9.

21. Eschenauer G, et al. Comparison of echinocandin antifungals. Ther Clin Risk Manag. 2007;3(1):71–97.
22. Andes DR, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis. 2012;54:1110–22.
23. Kollef M, et al. Septic shock attributed to Candida infections: importance of empiric therapy and source control. Clin Infect Dis. 2012;54:1739–46.
24. Eschenauer GA, et al. Fluconazole versus an echinocandin for Candida glabrata fungaemia: a retrospective cohort study. J Antimicrob Chemother. 2013;68:922–6.
25. Vazquez J, et al. Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial. BMC Infect Dis. 2014;14(97):1–10.
26. Perlin D. Echinocandin resistance in *Candida*. Clin Infect Dis. 2015;61(Suppl 6):S612–7.
27. Beyda ND, et al. Echinocandin resistance in Candida species: mechanisms of reduced susceptibility and therapeutic approaches. Ann Pharmacother. 2012;46:1086–96.
28. Mylonakis E, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis. 2015;60:892–9.
29. Pettit N, Carver P. Isavuconazole: a new option for the management of invasive fungal infections. Ann Pharmacother. 2015;49(7):825–42.
30. Isavuconazole (BAL8557) in the Treatment of Candidemia and Other Invasive Candida Infections. Astellas Pharma Inc.Available from: https://clinicaltrials.gov/ct2/show/NCT00413218?term=NCT00413218&rank=1. Accessed Sept 2016.

Chapter 4
Adjunct Corticosteroid Therapy for Patients with Community Acquired Pneumonia

Guy Handley and Ryan Sullivan

Introduction

Pneumonia remains a leading cause of morbidity and mortality worldwide [1], globally ranking third as a leading cause of death [2]. In the US, the disease is responsible for 1.1 million adult hospitalizations and 50,000 deaths each year [3, 4]. It is the most common antecedent to sepsis, occurring in nearly 50% of patients admitted with pneumonia [5], and the most common single cause of acute respiratory distress syndrome (ARDS) [6]. In fact, 10% of all hospitalizations for pneumonia lead to an ICU admission [7]. These characteristics make pneumonia a very expensive enterprise. In 2011, costs exceeded ten billion dollars, ranking as the seventh most expensive treated condition in US hospitals [8].

Despite numerous research initiatives aimed at improving antibiotic and treatment regimens, mortality rates have shown little to no improvements since the introduction of antibiotic therapy over 50 years ago [9]. Additionally, academic societies including the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS), the British Thoracic Society (BTS), and the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases (ERS/ESCMID) in the most recent published guidelines have only recommended empiric antibiotic therapies for treating patients diagnosed with community-acquired pneumonia (CAP) [10–12]. Typically pneumonia has been classified into specific groups that correlate to particular antibiotic regimes. None of these

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guidelines yet recommend any adjuvant therapy. Corticosteroid therapy has been scrutinized for much of the past half-century as a possible option [13]. Studies have demonstrated significant benefits from steroids in pulmonary diseases such as asthma [14] and COPD [15]. Additionally while once believed to be controversial, guided steroid therapy in infectious diseases such PJP pneumonia in HIV [16] and Streptococcus pneumoniae meningitis [17] has shown mortality benefit to the point it has become standard of care.

Defined as an infectious process of the lung parenchyma, pneumonia is thought to result from the invasion and overgrowth of microorganisms causing inflammation [18]. It is typically defined clinically as symptoms consistent with pneumonia such as cough, fever, dyspnea, or pleuritic chest pain in the setting of a new infiltrate on chest radiographic imaging. Throughout the disease process cells produce and distribute cytokines for clearing pathogens, repairing lung tissue and modulating the immune response [19]. Recently, elevated levels of specific cytokines, such as IL-6 and IL-10, have been shown to correlate with higher rates of mortality [20], possibly through disease progression to conditions such as sepsis [21] or ARDS [22]. Therefore, by suppressing the inflammatory reaction of pneumonia it may attenuate the severity of disease and generate more favorable outcomes.

Corticosteroids are among the most widely used drugs in the world and are considered one of the most effective anti-inflammatory therapies available [23]. They have previously demonstrated suppression of many of the cytokines involved in pneumonia pathophysiology [24]. Furthermore, low baseline cortisol levels have been linked to disease severity and lead to poorer outcomes in severe CAP [25]. In fact, one study found that most patients with severe CAP were co-diagnosed with relative adrenal insufficiency; however, it should be noted that they investigated a small number of patients and had a relatively high standard to define adrenal insufficiency [26]. This could suggest a benefit for corticosteroids as an adjunctive therapy to antibiotics.

Previous Studies

Beginning as early as the 1940s, studies had suggested a rapid fall of temperature and marked subjective improvement without worsening bacteremia or pulmonary consolidation in patients treated with ACTH, a stimulant for steroid production [27]. Many have measured decreased or attenuated inflammatory responses through biomarkers such as TNF-alpha, IL-1beta, IL-6 and C-reactive protein (CRP) measured by serum and bronchoalveolar lavage levels [28, 29]. Additionally, multiple RCTs and studies have demonstrated significant improvement in a number of outcomes including a reduction in hospital stay, duration of IV antibiotic courses, and time to clinical stability typically defined by improvement in respiratory status, vital signs or imaging in treatment arms receiving steroids [29–32].

Conversely, other RCTs have shown contrasting results including ones which showed no difference in clinical outcomes or mortality rates for CAP patients

treated with steroids [29, 33]. Additionally, a RCT by Snijders et al. uncovered a particularly concerning finding of increased rates of late respiratory failure, defined as return of symptoms over 72 h, after a reported improvement between the treatment arms ($p = 0.05$); however, this late failure phenomena was not demonstrated when stratifying for severe versus less severe pneumonia in the CURB-65 Score 3–5 or Pneumonia Severity Index (PSI) 4–5 populations.

Unfortunately, trials up until this point have been difficult to compare due to variations in patient populations and study design. Definitions for low-severity disease and high-severity disease have utilized various schemas including CURB-65 Score, PSI Score, or academic society definitions, but these are difficult to compare across studies. In addition markers such as IL-6, IL-10, TNF-alpha, IL-1beta, CRP have all been proposed as mediators of inflammation, but none have demonstrated utility as concrete indicators of severity of disease or predictors of clinical outcome. Most notably for actual clinical application, studies have been varied entirely on the type of steroid used, the dosage, and the duration of treatment.

CRP as a Biomarker

Although known to be associated with systemic inflammation, CRP until recently has not been utilized in protocol directed use of steroids in CAP in RCTs. It has, however, previously correlated with higher rates of treatment failure [34] and mortality [35]. The former of these two studies is a multicenter prospective cohort study also referred to as the Neumofail Group which investigated treatment failure risk factors in CAP, while the latter of these two studies investigated cystic fibrosis and bronchiectasis suggesting a role for CRP in patients with structural lung disease. In the latter study, CRP correlated with higher bacterial load and frequency of exacerbations, which could possibly be applied to community acquired pneumonia as well.

A multicenter, randomized, double-blind, placebo-controlled RCT by Torres et al. in 2015 utilized CRP as a biomarker with a clear separation of more-severe and less-severe CAP populations [36]. Only patients with severe CAP as defined by American Thoracic Society (ATS) or PSI Score V, and with CRP levels greater than 15 mg/dL were included. They reached this cut-off by selecting the 25th percentile of the population of patients with CAP and treatment failure demonstrated in the Neumofail Group [34].

Clear primary end-points were defined as *early treatment failure*, meaning the development of shock, the requirement for mechanical ventilation or death within 72 h, and *late treatment failure* defined by radiographic progression of respiratory failure, development of shock, the requirement for mechanical ventilation or death from 72–120 h. Results showed a decrease in treatment failure, especially late treatment failure, from 31 to 13% after a 5-day course of IV methylprednisolone (0.5 mg/kg per 12 h) added to antibiotic therapy. The author concluded that the acute use of methylprednisolone in patients with severe CAP and high inflammatory responses

decreases treatment failure. While other biomarkers have been proposed, and may later be shown to have benefit as possible tools to guide therapy, at this point CRP may be the most clinically useful biomarker in the treatment of CAP.

Pooled Analysis

Attempting to assess the inconsistencies reported by previous RCTs, Siemieniuk et al. in 2015 published a meta-analysis comprising 2005 patients across 13 RCTs conducted between 2010 and 2015, which evaluated steroids and CAP using the GRADE evidence criteria [37]. Their findings suggested that adjuvant systemic corticosteroid therapy for CAP led to an absolute reduction of 5% for the progression to ARDS and the need for mechanical ventilation with a corresponding number needed to treat (NNT) of 20. Furthermore, they showed with high certainty that steroids reduced time to clinical stability and duration of hospital stays by 1 day and that there was a possible reduction of mortality in patients diagnosed with severe CAP. The patient populations included in that distinction had to meet either PSI Score IV or V, Curb 65 Score greater than or equal to 2, or met ID/ATS criteria. The mortality benefit was only graded with moderate rather than high certainty due to a smaller number of events, subgroup modification and the effect of these differing definition criteria for more severe compared to less severe pneumonia. The authors additionally noted that in order to detect a relative reduction of mortality by 30%, an N of 3500 would be required. The primary side effect noted was a 6% increase in the need to treat hyperglycemia when using a corticosteroid but no long-term consequences were identified including no increased risk of GI bleed, neuropsychiatric reaction, or re-hospitalization.

Similarly, in the same year Horita et al. [38] published a meta-analysis of 10 RCTs comprising 1780 cases stating that adjuvant corticosteroids had also shortened the length of hospital stay and time to clinical stability. However, after a subgroup analysis, they found strong evidence for a mortality benefit with an NNT of 10. This was potentially limited in that the distinction of severe CAP was met if any of the RCTs were limited to ICU patients or utilized “severe CAP” in the title or abstract. While the RCTs included may have utilized more concrete scoring systems, the mortality benefit could be potentially confounded by this distinction. In addition they showed no difference in a short (less than or equal to 5 days) compared to a prolonged course (over 5 days) of steroids.

In 2016, Bi et al. [39] performed a meta-analysis to evaluate the efficacy and safety of adjuvant corticosteroids in patients only diagnosed with severe CAP. Analysis of 8 RCTs from 1993 to 2015 consisting of 528 severe CAP patients showed a significant reduction of all-cause mortality ($p = 0.003$), ARDS, and the need for mechanical ventilation. Severe CAP in this study was defined as PSI Score IV or V, Curb 65 Score greater than or equal to 2, or met ID/ATS criteria as well. Furthermore, they did not find that corticosteroids led to an increased frequency of hyperglycemia needing treatment like previous studies. Lastly, in a subgroup

analysis, they found corticosteroids reduced mortality most dramatically if taken for a prolonged time period (>5 days) which runs counter to the data found in the Horita meta-analysis.

Limitations

In addition to previously mentioned comparative distinctions across trials, pitfalls exist which increase the difficulty of distinguishing a patient population with CAP that could benefit from steroid adjunctive therapy. Types of pneumonia excluded in these studies were ventilator associated pneumonia (VAP), aspiration pneumonia, or hospital acquired pneumonia (HAP) which can be difficult to distinguish from CAP in the bedside setting. Non-infectious causes such as pneumonitis can also generate diagnostic uncertainty. In addition, much of the RCTs evaluating steroids and CAP exclude patients who had been considered at risk of steroid related complications including history of GI bleeding, pregnancy, immunosuppression, or concurrent use of steroids as an outpatient.

Recently a 2015 multi-center epidemiologic study by Jain et al. enrolled 2488 patients diagnosed at the bedside with CAP, who demonstrated both clinical signs and radiographic findings consistent with the disease [40]. The study collected cultures from blood, urine, and respiratory secretions combined with serologic testing, antigen detection, and molecular studies for various bacterial and viral pathogens. Patients were primarily excluded if they had immunosuppression or a recent hospitalization. Respiratory cultures accepted only included high-quality sputum samples, endotracheal aspirates, or bronchoalveolar lavage specimens. Importantly only 38% of patients had a pathogen identified. Among those viral infections by rhinovirus (9%) and influenza (6%) exceeded the incidence of *Streptococcus pneumoniae* (5%). No stratification by CAP severity or investigation of particular biomarkers was made in this study.

Viral pneumonia due to influenza presents a particular challenge. Lee et al. in 2015 in a pooled-analysis of 2649 patients in China from 2008–2011 with laboratory confirmed influenza A or B viral infection, suggested that systemic steroid use was associated with increased risk of mortality (p = 0.010, HR 1.73) [41]. Additionally a recent review by Nedel et al. [42] also concluded that corticosteroids failed to show any benefit in severe influenza pneumonia and is likely to increase mortality.

On the other hand, another recent meta-analysis of this topic by Rodrigo et al. speculated that the decisions to give steroids were made by the physician at the bedside, and those who received steroids in this study may have had more severe infections and a greater risk of mortality prior to treatment, rather than a true effect from steroids themselves [43]. They too found an association with increased mortality in observational studies but critically noted no RCTs have been performed on this topic. Nevertheless, corticosteroid therapy in viral pneumonia is poorly understood at this point and could potentially impact outcomes in those diagnosed with CAP.

Future Trials

Currently, two clinical trials are underway that may help clarify how steroids could be utilized as an adjunct to CAP. The ESCAPe trial (NCT01283009) [44] is a double-blinded phase III RCT run by the Veterans Association of Research and Development. Patients (n = 1450) with severe CAP as defined by ATS criteria will be randomly assigned to adjunctive administration of a tapering bolus dose of methylprednisolone or placebo for 20 days. Patients will be followed for 180 days and assessed for all-cause 60-day mortality as a primary outcome. The estimated completion date was January 2017.

The CAPE_COD trial (NCT02517489) [45] is a double-blinded phase III RCT being conducted in France. Patients (n = 1200) with severe CAP are defined by a pneumonia severity index >130 (Score V), the requirement of mechanical ventilation, or the need for high-flow oxygen therapy of FiO2 of 50% or less than a PaO2/FiO2 ratio of 200. Patients will be assigned to adjunctive IV hydrocortisone therapy of 8 or 14 days of a tapering dose of continuous IV infusion starting at 200 mg/day. The primary outcome is 28-day all-cause mortality. The study is estimated to be completed in December 2018.

Applying Corticosteroids to Clinical Practice

Despite notable discrepancies including definitions for low-severity disease and high-severity disease, which biomarkers have clinical utility, and the appropriate dose and duration of steroids, the available evidence at this point suggests that at least for the most severe cases of CAP, steroids likely provide a benefit in mortality, duration of hospitalization, and reduction in incidence of disease related complications such as ARDS or need for mechanical ventilation. These conclusions may have massive implications for the large amount of patient suffering and economic burden attributed to pneumonia.

Current algorithms, such as that by Torres and Cilloniz, emphasize both biomarkers and severity of illness when recommending adjunctive therapy with corticosteroids [46]. We would agree with the proposed algorithm by Torres and Cilloniz, but propose a more restricted application (Fig. 4.1) at this current time. We believe this algorithm below currently has enough evidence to suggest the potential benefits of corticosteroid administration outweigh the risks of therapy. Until further studies, particularly RCTs, can demonstrate which exact populations may benefit from steroids in CAP, which, if any, biomarkers have a clinical utility, and which steroid treatment regimen provides the greatest benefit, corticosteroids as an adjunctive therapy for CAP cannot yet be recommended to be incorporated into the standard of care. We acknowledge that this algorithm cannot be utilized as a substitute for clinical judgement and does not yet identify which patient population will benefit most from corticosteroid therapy. As such future studies need more power with a larger

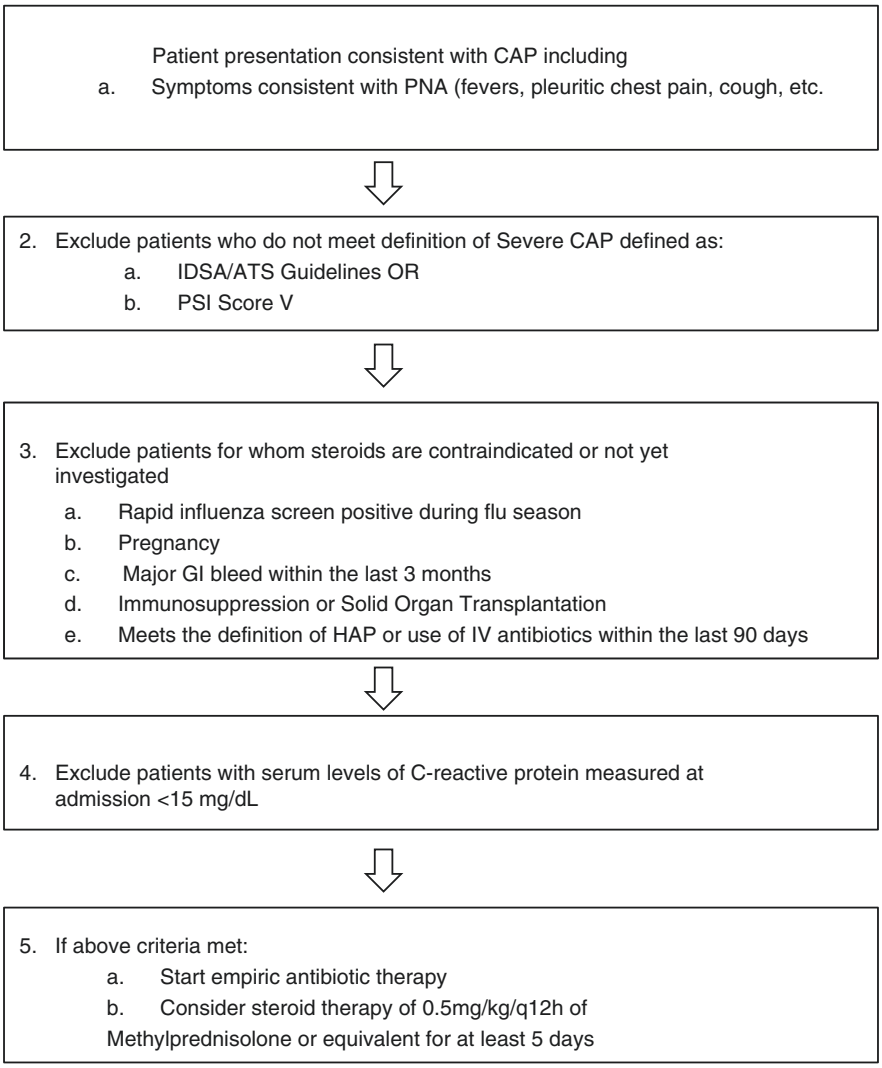

Fig. 4.1 Proposed Algorithm for Corticosteroid Use in Community Acquired Pneumonia

more defined patient population. Efficacy, safety, and side effects need to be assessed in cohorts such as pregnant women, immunodeficient patients, chronic corticosteroid users, and those with varying comorbidities which could potentially also benefit from steroid therapy. Corticosteroids likely provide benefit to patients with severe cases of community acquired pneumonia and can be utilized when clearly indicated; however, there remains much investigation to be undertaken before it can be fully incorporated the standard of care for community acquired pneumonia.

Key Points

- Empiric antibiotics continue to be the primary recommendation for treatment of community acquired pneumonia, despite no substantive change in mortality rates over the last 50 years. To date the utility of adjunctive therapies has not been fully demonstrated.
- Corticosteroids have already demonstrated significant benefits in obstructive lung disease as well as other infectious processes, and have been investigated as an adjunctive therapy for community acquired pneumonia for several decades with mixed results.
- Many biomarkers have been proposed to as indicators of severity of disease or predictors of clinical outcome to identify who might benefit from corticosteroids; however, C-reactive protein appears to show the most promise and has been demonstrated to correlate with higher rates of treatment failure and mortality.
- The most recent clinical trials and meta-analysis suggest that for the most severe cases of community acquired pneumonia (PSI IV-V or meeting IDSA/ATS guidelines), patients who receive corticosteroids have improvements in mortality, duration of hospitalization, and a reduction in incidence of disease related complications such as ARDS or need for mechanical ventilation. These populations should be strongly considered for adjunctive steroid therapy in clinical practice.
- Future investigations should focus on improving distinctions of low-severity disease and high-severity disease, which biomarkers have clinical utility as well as how to implement them, and the appropriate dose and duration of steroids before their use can be recommended as standard of care for all types of community acquired pneumonia.

References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459–544.
2. WHO. The top 10 causes of death. 2014. December 1, 2016; Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.
3. Pfuntner A, Wier LM, Stocks C. Most Frequent Conditions in U.S. Hospitals, 2011: Statistical Brief #162, in Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville, MD: Agency for Healthcare Research and Quality; 2006.
4. Kochanek KD, et al. Deaths: final data for 2014. Natl Vital Stat Rep. 2016;65(4):1–122.
5. Dremsizov T, et al. Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest. 2006;129(4):968–78.
6. Estenssoro E, et al. Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. Crit Care Med. 2002;30(11):2450–6.

7. Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. Medicine (Baltimore). 2007;86(2):103–11.
8. Torio CM, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011: Statistical Brief #160, in Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville, MD: Agency for Healthcare Research and Quality; 2006.
9. Mortensen EM, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med. 2002;162(9):1059–64.
10. Mandell LA, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.
11. Lim WS, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):iii1–55.
12. Woodhead M, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clin Microbiol Infect. 2011;17(Suppl 6):E1–59.
13. Reeder WH, Mackey GS. Nebulized cortisone in bacterial pneumonia. Dis Chest. 1950;18(6):528–34.
14. Kroegel C, Wirtz H. History of guidelines for the diagnosis and management of asthma: from opinion to control. Drugs. 2009;69(9):1189–204.
15. Hurd S, Pauwels R. Global initiative for chronic obstructive lung diseases (GOLD). Pulm Pharmacol Ther. 2002;15(4):353–5.
16. Gagnon S, et al. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med. 1990;323(21):1444–50.
17. Lebel MH, et al. Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. N Engl J Med. 1988;319(15):964–71.
18. Alcon A, Fabregas N, Torres A. Pathophysiology of pneumonia. Clin Chest Med. 2005;26(1):39–46.
19. Bordon J, et al. Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective versus deleterious inflammatory response in pneumonia. Int J Infect Dis. 2013;17(2):e76–83.
20. Martinez R, et al. Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. Eur Respir J. 2011;37(2):393–9.
21. Hack CE, et al. Increased plasma levels of interleukin-6 in sepsis. Blood. 1989;74(5):1704–10.
22. Meduri GU, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest. 1995;107(4):1062–73.
23. Barnes PJ. How corticosteroids control inflammation: quintiles prize lecture 2005. Br J Pharmacol. 2006;148(3):245–54.
24. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med. 2005;353(16):1711–23.
25. Salluh JI, et al. Adrenal response in severe community-acquired pneumonia: impact on outcomes and disease severity. Chest. 2008;134(5):947–54.
26. Salluh JI, et al. Cortisol levels in patients with severe community-acquired pneumonia. Intensive Care Med. 2006;32(4):595–8.
27. Lewis GM, Davis GM, Waldriff GM. PROCEEDINGS of the first clinical ACTH conference. Postgrad Med. 1950;7(5):376–7.
28. Monton C, et al. Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. Eur Respir J. 1999;14(1):218–20.
29. Snijders D, et al. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med. 2010;181(9):975–82.
30. Confalonieri M, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med. 2005;171(3):242–8.

31. Fernandez-Serrano S, et al. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. Crit Care. 2011;15(2):R96.
32. Blum CA, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2015;385(9977):1511–8.
33. Meijvis SC, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377(9782):2023–30.
34. Menendez R, et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax. 2009;64(7):587–91.
35. Chalmers JD, et al. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2012;186(7):657–65.
36. Torres A, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA. 2015;313(7):677–86.
37. Siemieniuk RA, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. Ann Intern Med. 2015;163(7):519–28.
38. Horita N, et al. Adjunctive systemic corticosteroids for hospitalized community-acquired pneumonia: systematic review and meta-analysis 2015 update. Sci Rep. 2015;5:14061.
39. Bi J, et al. Efficacy and safety of adjunctive corticosteroids therapy for severe community-acquired pneumonia in adults: an updated systematic review and meta-analysis. PLoS One. 2016;11(11):e0165942.
40. Jain S, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373(5):415–27.
41. Lee N, et al. Neuraminidase inhibitors, superinfection and corticosteroids affect survival of influenza patients. Eur Respir J. 2015;45(6):1642–52.
42. Nedel WL, et al. Corticosteroids for severe influenza pneumonia: a critical appraisal. World J Crit Care Med. 2016;5(1):89–95.
43. Rodrigo C, et al. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2016;3:Cd010406.
44. VA Office of Research and Development. CSP #574—Evaluate the safety and efficacy of methylprednisolone in hospitalized veterans with severe community-acquired pneumonia. 12/6/2016; Available from: https://clinicaltrials.gov/ct2/show/NCT01283009.
45. University Hospital T. Effects of low-dose corticosteroids on survival of severe community-acquired pneumonia. 09/05/2017; Available from: https://clinicaltrials.gov/ct2/show/NCT02517489.
46. Torres A, Cilloniz C. Severe community-acquired pneumonia: corticosteroids as adjunctive treatment to antibiotics. Community Acquir Infect. 2016;3:1–3.

Chapter 5
Procalcitonin and New Biomarkers

N.A. Mir, D. Ho, J. Toews, and J. Walsham

Abbreviations

CALC-1	Caclitonin-1
CAP	Community acquired pneumonia
CCP-1	Calcitonin carboxyl-terminus peptide-1
CRP	C-reactive protein
HAP	Hospital acquired pneumonia
IDSA	Infectious diseases society of America
LIA	Laser light scattering immunoassay
PCT	Procalcitonin
PCT-Q	Procalcitonin qualitative assay
PRORATA	Procalcitonin to reduce patients' exposure to antibiotics
SISPCT	Sodium selenite and procalcitonin guided antimicrobial therapy in severe sepsis
SOFA	Sequential organ failure assessment score
VAP	Ventilator-associated pneumonia
WBC	White blood cell
WCC	White cell count

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Introduction

Biomarkers are useful in hospital practice because they may aid in both diagnosing and predicting the progression of disease. Biomarkers are also adjuncts to disease management as they help monitor the success of therapeutic interventions and provide the patient with a more personalized management [1]. Despite their convenience, biomarkers come with costs. While they aid with risk stratification and may improve patient outcomes, they also significantly contribute to rising healthcare costs. Inappropriate ordering and interpretation of biomarkers may result in unnecessary patient imaging, hospitalization, and procedures [2].

The timely and accurate identification of sepsis is an important skill for the hospitalist. It has been demonstrated that traditional indicators of sepsis such as the SIRS criteria are neither sensitive nor specific for infection [3]. The revised definition of sepsis has been demonstrated to more accurately define a population at increased risk of death but similarly does not accurately define a septic patient. Biomarkers such as CRP and WBC count have been utilized by clinicians to diagnose sepsis, but over the last 25 years procalcitonin (PCT) has increasingly been utilized to identify patients with bacterial sepsis.

Studies have evaluated patients in outpatient and hospital settings and patients with different septic syndromes. PCT has been used to determine when to commence and when to cease antibiotic therapy. It may be utilized to prognosticate and studies have also evaluated whether PCT-guided antibiotic therapy may lead to reduced mortality. We review the background of PCT, the body of literature regarding PCT, with a focus on the last few years, as well as provide an overview of other biomarkers of interest to the hospitalist.

Procalcitonin

PCT is released in the bloodstream of healthy individuals at levels of less than 0.05 ng/L. [4] Following stimulus by a bacterial endotoxin, PCT plasma concentration rises within 2–3 h after bacterial invasion. PCT levels plateau after 6–12 h and remain high for up to 48 h before falling to baseline within the following 2 days [5]. This rapid and persistent response to bacterially induced systemic inflammation highlights PCT's role as a marker of sepsis. PCT can be present in the circulation for up to 7 days but after removal of an inflammatory signal like bacterial endotoxin, the half-life is around 20–35 h [5, 6]. In comparison, CRP is detectable 4–6 h post inflammation and peaks 36–50 h with a half-life of 19 h after the stimulus is removed [6, 7] (see Figs. 5.1 and 5.2).

No specific route of elimination of PCT has yet been established. It is postulated that it is degraded by proteolysis like other plasma proteins. Renal excretion plays a minor role [7].

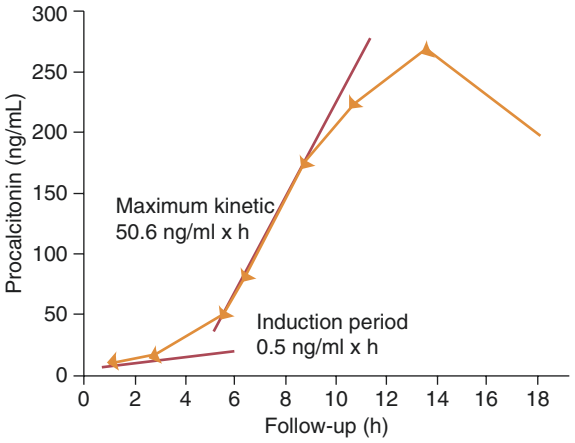

Fig. 5.1 Displays the kinetics of PCT following the introduction of bacterial endotoxin [5]

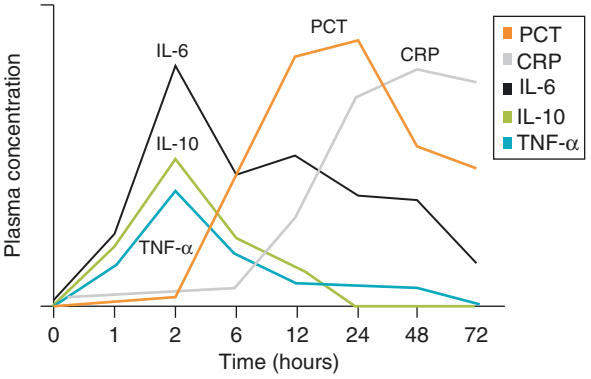

Fig. 5.2 Displays PCT in comparison to other markers of inflammation [5]

Measurement of Procalcitonin

PCT is measured via immunoassay techniques standardized to the original Brahms PCT Luminescence Immunoassay. The automated PCT assays used in hospital differ largely in the detection method of the antibody-PCT-antibody complex and individual characteristics of the assays, and are all standardized to the BRAHMS LIA assay. Semiquantitative point of care PCT testing also exists. The Brahms PCT-Q uses immunochromatography to produce a reddish/brown band that can be classified by comparison with a color card into four PCT levels (<0.5, 0.5–2.0, 2.0–10 and >10 ng/mL). 200 μL of serum or plasma is used and results are generated within an hour [4] (see Table 5.1).

Table 5.1 Summarizes the different PCT assays for serum/plasma used in hospital [4]

Company	Assay platform	Assay principle	Measuring range (ng/mL)	Functional sensitivity (ng/mL)	Detection limit (ng/mL)	Time (min)
Brahms	Kryptor, Kryptor compact, Kryptor compact plus	Immunofluorescence	0.02–5	0.06	0.019	19
Roche	Elecsys	Electrochemiluminescence	0.02–100	0.06	<0.02	18
	Modular					
	Cobase					
Siemens	Advia centaur/AP	Chemiluminescence	0.02–75	<0.05	<0.02	26–29
	Centaur CP					
BioMerieux	Vidas	Enzyme-linked fluorescence	0.05–200	0.09	0.05	20
	Minividas					
Diasoria[a]	Liasion	Chemiluminescence	0.1–500	<0.24	<0.032	

Measuring range—range of procalcitonin levels obtainable without diffusion; functional sensitivity—lowest concentration measured with a coefficient of variation of <20%; detection limit—lowest concentration differing from zero with a 95% probability

[a]Currently not marketed in the UK

Physiology of Procalcitonin

PCT's biological function is unclear. It has been reported to possess both pro- and anti-inflammatory properties. Its immunological role may be as a co-factor capable of modulating the impact of endotoxin shock. It is upregulated in response to pro-inflammatory mediators such as IL-1b, TNF-α, and IL-6. Some studies suggest that serum PCT decreases in response to cytokines (like interferon-gamma) released during a viral infection [8]. Some studies have suggested it has an influence on cytokine and nitric oxide (NO) expression but this has not translated to in vivo studies. PCT may also have a role in sepsis mortality [9]. Improved survival rate of animal models was found when endogenous PCT was neutralized. Moreover, the exogenous administration of PCT to septic animals resulted in an increase in mortality. In vitro studies have also shown a reduction in thromboxane B2 with the introduction of PCT [10].

Recommendations Surrounding the Use of Procalcitonin

Sepsis

PCT May Be Useful in Differentiating Sepsis from SIRS

PCT was first found to be a useful adjunct to sepsis guidelines in 2006 where PCT acted as a good diagnostic marker for sepsis, severe sepsis, and septic shock for

critically ill patients where the diagnosis was clear (based off a systematic review and meta-analysis of 33 studies) [11]. Nevertheless, a later meta-analysis by Tang et al. in 2007 showed that PCT could not accurately differentiate sepsis from SIRS in critically ill adult patients from a variety of settings including medical, surgical, ICU, emergency departments, and hospital wards. The latest Surviving Sepsis Campaign guidelines from 2012 state that the utility of PCT levels in differentiating sepsis versus other causes of inflammation (e.g., postoperative, other forms of shock) has yet to be proven [12].

More recently, however, a meta-analysis has come out that perhaps there is a role for PCT in diagnosis—as a rule-out tool. In an analysis of 30 studies, Wacker et al. [13] found that elevated PCT levels indeed suggest sepsis, and that low PCT levels should discourage initiation of antibiotics. However, they were unable to recommend a specific cutoff score, and that PCT levels must be interpreted in the clinical context [13]. A more recent meta-analysis defined a specific cutoff level of 0.5 mg/dL, and found that it was most useful and accurate in diagnosing sepsis in ICU patients, but performed the worst in immunocompromised patients. Their recommendation is that low PCT levels should help to rule out the presence of bacteremia [14].

As it stands, the literature is pointing towards PCT being used as a rule-out tool for sepsis—if PCT levels are low, sepsis is less likely. However, a high PCT level does not equate to a patient having bacteremia or sepsis. It still remains that any PCT levels should be interpreted with caution, and with the clinical context in mind.

PCT Serial Measurements Can Predict Sepsis Mortality

An early RCT conducted by Shehabi et al. found that a slow PCT decline over the first 72 h was an independent predictor of hospital and 90-day all-cause mortality [15]. A recent meta-analysis, building on this RCT, found that both elevated PCT concentrations and PCT nonclearance were strongly associated with all-cause mortality in septic patients. However, once again, no specific cutoffs were suggested, as they were unable to analyze the raw patient data, and the definition of "nonclearance" varied greatly between studies [16].

PCT Can Help Reduce Antibiotic Exposure in Patients with Sepsis

Perhaps most promising is the potential for PCT levels to guide cessation of antibiotics, thus reducing overall antibiotic exposure. Of course, this has to be balanced with the risk of reinfection or sub-optimal clearance of infection. This was analyzed in the multicenter prospective parallel group open-label study called the PRORATA study [17], which was one of the first studies to specifically look at using PCT to reduce antibiotic exposure in adults in the ICU with suspected bacterial infections. Antibiotics were ceased when PCT was <80% of the patient's peak concentration or when the absolute PCT < 0.5 μg/L. The study showed that a PCT-guided antibiotic treatment substantially lowered antibiotic exposure and was non-inferior to standard care with respect to patient outcomes. The difference was around 2.7 days that corresponded to a 23% relative reduction in antibiotic exposure by day 28 [17].

Table 5.2 Summarises the PCT's use and validity in sepsis diagnosis and management

Sepsis				
Authors	Sepsis indication	Sensitivity	Specificity	Relative risk
Hoeboer et al. [14]	Sepsis diagnosis (0.5 mg/dL cutoff)	76%	60%	
Wacker et al. [13]	Antibiotic initiation	77%	79%	
Liu et al. [16]	Risk of death and elevated PCT	76%	64%	2.60 (2.05–3.30)
Liu et al. [16]	Risk of death and PCT nonclearance	72%	77%	3.05 (2.35–3.95)
Bouadma et al. [17]	Risk reduction of antibiotic exposure			23%

Several recent studies have evaluated the efficacy and safety of PCT-guided antibiotic therapy in patients with sepsis and have confirmed that PCT use is associated with a reduction in antibiotic exposure across multiple settings without significantly impacting mortality [18–21]. Nevertheless, this view has not been shared by other studies using PCT-guided algorithms [15, 22]. Despite these studies showing nil effect, more recently, as a follow-up to the PRORATA trial, the largest and most recent de Jong et al. trial randomized 1575 patients who were admitted to the ICU with suspected infection to PCT-guided cessation of antibiotic therapy—when the PCT had fallen by 80% from its peak measured value or had fallen to below 0.5 μg/mL. The study showed not only reduced antibiotic exposure in the PCT group, but also an associated reduction in 28-day mortality [23].

These results all suggest that the use of PCT-guided antibiotic therapy leads to decrease in antibiotic therapy without compromising patient safety in the critically ill. This has several benefits—firstly, this reduces use of antibiotics, which helps with antimicrobial stewardship. Secondly, this reduces the overall cost of healthcare, as prescription rates are decreased.

See Table 5.2 for a summary of PCT's use in sepsis management.

Respiratory Infections

Community Acquired Pneumonia

PCT Can Help in Ruling Out Bacterial Pneumonia

A 2012 systematic review of the role in PCT in adults with CAP found that PCT levels in those with typical pneumonia were significantly higher than in those with atypical or viral pneumonia [24]. The 2013 Cochrane review by Schuetz et al. (2013) found that in the primary care setting, PCT is useful for ruling out acute respiratory illnesses overall [25]. The procalcitonin level recognized by recent 2016 studies is a cutoff of 0.25 μg/L where levels below 0.25 μg/L make bacterial infection unlikely, and levels below 0.1 μg/L make bacterial infection highly unlikely [26].

PCT May Help Predict the Severity of CAP and Correlate with Long Term Outcomes

Earlier systematic reviews have also found PCT to correlate well with predictors of severity, like the Pneumonia Severity Index and the CURB65 scoring system [24]. A multi-center prospective trial even recommended that an on-admission PCT > 0.35 ng/mL was the most accurate predictor of early ICU admission [27]. Furthermore, on-admission PCT could help predict 28-day mortality [28, 29]. PCT levels <0.229 ng/mL had a 99% predictive value that patient would not die, despite having a high CURB-65 score. This allows PCT to act as a decisive factor on who can safely be treated as an outpatient [28]. PCT, when added to the predictive value of prognostic scoring tools, was found to be more useful than when the same was done with CRP. Treatment failure was also found to be higher in patients with a higher PCT on day 1 [29]. Nevertheless, the most recent 2016 meta-analysis by Nobre et al. showed that inpatients with CAP in emergency units had differing data. Although low levels of PCT could increase confidence of keeping CAP patients outside of ICU, it did not exceed the performance of the CURB-65 or other clinical scores [30].

PCT Can Help Determine the Optimal Duration of Antibiotic Therapy in CAP

Large randomized controlled trials that set out to define the duration of antibiotic therapy by measuring PCT at various time points showed a reduction in the median duration of treatment [31–33]. In addition, the use of PCT-guided algorithms has not been associated with increased mortality or treatment failure in any clinical setting, or acute respiratory infection diagnosis [34]. Furthermore, a 2011 meta-analysis found PCT-guided therapy to be safe and could help reduce the length of hospital stay without impacting disease outcome [35]. A 2016 meta-analyses provided useful data surrounding measurements of PCT that guide when antibiotics should be started. Levels between 0.25 and 0.50 μg/L suggest that infection is likely, and antibiotic therapy was recommended. Levels above 0.5 μg/L makes bacterial infection highly likely, with a strong recommendation for antibiotics (see Table 5.3) [26].

Table 5.3 Provides the recommendations for PCT-guided antibiotic initiation in adults with respiratory infections [26]

Procalcitonin level (μg per L)	Recommendation
<0.10	Bacterial infection highly unlikely; strongly recommend against antibiotics
0.10 to <0.25	Bacterial infection unlikely; recommend against antibiotics
0.25 to 0.50	Bacterial infection likely; recommend antibiotics
>0.50	Bacterial infection very likely; strongly recommend antibiotics

Note: Algorithm for discontinuation of antibiotic therapy was more variable, with many studies recommending discontinuation when procalcitonin levels were decreased by 80–90% from baseline level or were <0.25 μg per L

As for discontinuation decisions, the IDSA guidelines suggest PCT levels *is* useful, when used with clinical criteria. It has repeatedly been found that procalcitonin-guided antibiotic therapy leads to less days of antibiotic therapy. This remains a weak recommendation, however, as many of the studies were based on VAP patients making it unclear whether this also applies to HAP or CAP. In addition, many of the control groups in the trial routinely received antibiotics for 9–15 days, but it is unclear whether the reduction in antibiotics would still be present if routine care had lower baseline duration of antibiotic therapy [36]. Cutoff levels to trigger cessation of antibiotics has been highly variable between studies, but many studies recommend discontinuing antibiotics when PCT levels decreased by 80% from baseline level, or when PCT levels are <0.25 μg/L [26].

Hospital/Ventilator Acquired Pneumonia

PCT Can Help Guide Antibiotic Use in HAP/VAP

In patients with VAP or HAP, the most recent guidelines suggest that PCT should not be used in judgement for starting antibiotics, but can assist in discontinuation decisions, much like in the critically ill population [36].

A 2009 multicenter RCT of 101 patients with VAP helped define some of the cutoffs necessary for antibiotic cessation. The following criteria were used:

1. A PCT of <0.25 μg/L suggested VAP absence and antibiotic discontinuation
2. A PCT between 0.25 and 0.5 μg/L or a PCT drop >80% from day 0 meant that the infection was likely and antibiotic reduction was encouraged.
3. A PCT >0.5 μg/L or decrease <80% compared with day 0 discouraged antibiotic cessation.
4. A PCT > 1 μg/L strongly suggested antibiotic cessation not be done.

The trial observed a benefit of incorporating PCT to their current antibiotic cessation plan, as their average number of antibiotic free days alive was 27% higher for patients who had been randomized to PCT than of the control. Furthermore, the PCT group did not fare differently in terms of evolution of disease, number of ventilator free days alive, number of ICU free days alive, length of hospital stay, and overall mortality. Long-term use of broad-spectrum antibiotic use may also have been avoided [37].

PCT Might Help Predict the Prognosis of VAP

Prognostic value of serum PCT was assessed in a prospective observational study in a medical ICU looking at patients with VAP. Serial PCT at days 1, 3, and 7 was measured. The poor outcomes included death, persistent infection, relapse, and pulmonary or extra-pulmonary super infection. Serum PCT was higher in patients with poor outcomes and a serum PCT cutoff of 0.5 ng/mL on day 7 was the strongest predictor of a poor outcome regardless of the clinical presentation of VAP. This proved to be better than WBC and CRP measurements. Also VAP patients with a poor outcome also had higher PCTs on Day 1. This was most likely due to differences in baseline characteristics and PCTs association with more severe disease [38].

Bacterial Co-infection with Influenza

PCT Could Help Rule Out the Presence of Bacterial Co-infection in Influenza Patients

In a 2013 meta-analysis of adults with H1N1 influenza infection, 137 cases of influenza with bacterial confection were identified. PCT was assessed alone or compared with other biomarkers in its ability to identify secondary bacterial infections. PCT was found to elicit poor ability to rule in bacterial co-infection but had great diagnostic ability to rule out bacterial co-infection (NPV = 90%) [39]. Another slightly larger 2014 meta-analysis of 161 H1N1 patients that also looked at PCT's diagnostic role in bacterial co-infection, similar results were found. At an overall PCT cutoff >0.5mcg/L, PCT was able to rule out bacterial infection with a sensitivity of 85.5%.

Other Respiratory Illnesses

PCT Could Help Reduce Antibiotic Exposure in Acute Bronchitis

A Cochrane review assessed PCT's use in starting and stopping antibiotics for patients with acute respiratory infections including bronchitis. 14 trials with 4221 patients from multiple clinical settings were included, and it was found that PCT-guided decision-making resulted in a drop in the median days of antibiotic exposure (from 8 days to 4 days) without increasing the 30-day treatment failure or mortality [25]. An earlier review defined a cutoff range from <0.1 to <0.25 μg/L when determining the need for antibiotics. Overall (including low, moderate, and high acuity diseases) there was no significant difference in mortality. There was also a reduction in antibiotic prescription and/or duration of therapy [18].

PCT in Other Respiratory Conditions—Asthma, Idiopathic Pulmonary Fibrosis (IPF), Aspiration Pneumonia, and Congestive Cardiac Failure (CCF)

(a) *Asthma and IPF*: Two studies evaluated PCT in asthma patients with exacerbations; both studies demonstrated reduced commencement of antibiotics in the PCT-guided group. Long et al. evaluated hospitalized patients and also demonstrated reduced total exposure to antibiotics [40] whilst Tang et al. assessed patients at ED presentation and demonstrated a correlation between PCT and severity of asthma exacerbation [41]. Ding et al. found similar results in an IPF population with reduced antibiotic prescription and duration [42].
(b) *Aspiration Pneumonia*: Ogasawara determined the duration of treatment for hospitalized aspiration pneumonia patients based upon the initial PCT level and demonstrated reduced duration of antibiotics [43].
(c) *CCF*: Schuetz performed a secondary analysis of the ProHOSP study, an RCT of PCT-guided therapy for patients presenting with LRTI, looking at CCF patients [8]. Patients presenting with acute heart failure had a higher mortality if they had an elevated PCT and were not treated with antibiotics [44].

Furthermore, patients diagnosed with acute heart failure that had a low PCT and who were treated with antibiotics also had a higher mortality when compared to their untreated comparators. Mechanistically, it is proposed that the treatment of heart failure patients for potential sepsis may include unnecessary intravenous fluids, which may be harmful, and that PCT may help distinguish non-infected patients [8].

(d) See Table 5.4 for highlights where PCT has proven to be a useful adjunct to Diagnosis, Management, and Prognosis of Respiratory infections in the community and in those with comorbid cardiopulmonary disease.

Table 5.4 Highlights where PCT has proven to be a useful adjunct to diagnosis, management, and prognosis of respiratory infections in the community and in those with comorbid cardiopulmonary disease

Respiratory illnesses								
Authors	Indication	Sensitivity	Specificity	PPV	NPV	Odds ratio / hazard ratio	Relative risk	Overall change
Morris et al. [26]	CAP diagnosis (0.25 μg/L)	98%						
Schuetz et al. [25]	Reduction in duration of antibiotic exposure in CAP					3.98 (4.44–3.52)		
Stolz et al. [37]	Reduction in duration of antibiotic exposure in HAP/VAP							27%
Luyt et al. [38]	PCT of 0.5 ng/mL on day 7 as a poor prognostic factor in HAP/VAP	90%	88%			64.2 (11.1–375.5)		
Wu et al. [39]	Rule out bacterial co-infection in influenza	84%	64%	50%	90%			
Schuetz et al. [18]	Overall difference in mortality when using PCT to discontinue antibiotics in acute bronchitis of varying severity					0.91 (0.73–1.14)		

(continued)

Table 5.4 (continued)

Respiratory illnesses								
Authors	Indication	Sensitivity	Specificity	PPV	NPV	Odds ratio / hazard ratio	Relative risk	Overall change
Long et al. [40]	Reduction in antibiotic exposure in asthma exacerbation						0.56 (0.44–0.70)	44.3%
Ding et al. [42]	Reduction in antibiotic exposure in IPF exacerbation (0.25 ng/ml)							5.8 days median reduction
Ogasawara et al. [43]	Reduction in antibiotic exposure in aspiration pneumonia							3 days median reduction
Maisel et al. [44]	Antibiotic initiation and cessation in acute heart failure (PCT of 0.21 and 0.05 ng/mL, respectively)							Impact on survival

Burns

PCT Has Little Use in the Diagnosis and Prognosis of Sepsis in Burns Patients

Sepsis is a common cause of death in burns patients, and yet it is difficult to diagnose, as the usual inflammatory markers such as CRP are all elevated in burns patients, making it difficult to distinguish between normal inflammation and true sepsis. PCT has shown mixed results supporting its role in diagnosing sepsis in burns patients and it has not been shown to report significant clinical benefit [45, 46].

Other Indications

Given PCT success with bacterial infections, it has been tested across a myriad of other indications. Some not so successful indications include diagnosing infective endocarditis and infection in hematopoietic stem cell transplant recipients [47]. PCT has been found to positively correlate with severity of acute pancreatitis at values above 0.5 ng/mL. Nevertheless, PCT is nonspecific and an elevation is not

useful at isolating the source of infection and should thus be used as an adjunct to conventional severity stratification and as a guide to disease progression [48].

A PCT cutoff of 0.5 ng/mL can also be used to rule in bacterial infections in patients with autoimmune disease [49]. At even lower cutoffs of 0.2–0.3 ng/mL, PCT has a 90% sensitivity in ruling out septic arthritis and osteomyelitis. This was found to be superior to CRP as well [50]. For infectious parapneumonic effusions however, PCT was found to have as much diagnostic utility as CRP even when sampled from pleural fluid [51]. While PCT was not found to be useful for diagnosing acute appendicitis PCT was found to be useful in diagnosing complicated appendicitis (sensitivity 62%, specificity 94%) implying its usefulness in diagnosing severity [52]. In adults, PCT has been found to be an excellent diagnostic tool in multiple meta-analyses in the past 2 years in differentiating bacterial meningitis from viral meningitis in adults and in children [53–55]. It is also an excellent tool at ruling in and ruling out bacterial infections in patients with liver cirrhosis at cutoffs as low as 0.42 ng/mL [56] PCT has also been investigated in the diagnosis of bacterial infections in chronic renal insufficiency patients as well, but the results so far are disappointing [57]. See Table 5.5 for a complete list of studies where PCT has an indication for use.

New Biomarkers

A large number of biomarkers have been investigated for clinical uses with promise shown for diagnostic, prognostic, and therapeutic uses in inflammatory conditions and organ systems. There is a major focus in both current research and clinical practice in differentiating infectious from non-infectious processes. This section will briefly talk about other biomarkers which have been used to diagnose sepsis such as IL-6, IL-8, LBP, and presepsin.

IL-6 is a 26 kDa cytokine which is produced by hepatocytes, megakaryocytes, and a large number of leukocyte subpopulations in response to a variety of insults such as infection and inflammation [58]. IL-6 promotes fever as a well-known pyrogen and functions to promote the acute phase response through production of large numbers of acute phase proteins which include CRP and ferritin. There is no universally agreed upon half-life for IL-6, with estimates ranging from between 2 and 15 h—this is likely in part due to the complex interdependence of IL-6 on a number of regulating factors which influence its serum concentration and availability which are not yet fully understood [58–60]. IL-6 accumulates quite rapidly for at least 2 h in an early inflammatory phase (before CRP does) and in a manner proportional to severity—for example around 150 ng/mL for conditions like rheumatoid arthritis and into the low ug/mL ranges for severe sepsis [58–61]. It is present quite transiently and then declines quickly following removal of the insult with some studies

Table 5.5 Depicts the various systemic illnesses that PCT could be utilized

Other indications								
Authors	Indication	Sensitivity	Specificity	(+) Likelihood ratio	(−) Likelihood ratio	Odds ratio/ hazard ratio	Relative risk	Overall change
Mofidi et al. [48]	Prediction of severe acute pancreatitis (0.5 ng/mL)	72%	86%			14.9 (5.6–39.8)		
Mofidi et al. [48]	Prediction of infected pancreatic necrosis (0.5 ng/mL)	80%	91%			28.3 (13.8–58.3)		
Wu et al. [49]	Diagnosis of bacterial infection in patients with autoimmune disease	75%	90%	7.28 (5.10–10.38)	0.28 (0.18–0.40)			
Shen et al. [50]	Diagnosis of septic arthritis and osteomyelitis	67%	90%	6.48 (2.28–14.6)	0.37 (0.16–0.84)			
Yu et al. [52]	Diagnosis of complicated acute appendicitis	62%	94%					
Wei et al. [55]	Diagnosing bacterial meningitis	97%	95%	31.7 (8.0–124.8)	0.06 (0.03–0.11)	568 (103–3141)	0.56 (0.44–0.70)	
Lin et al. [56]	Diagnosing bacterial infection in cirrhosis	79%	89%	7.38 (4.70–11.58)				

suggesting it disappears to undetectable levels within 24 h [62]. IL-6 may play a future role in diagnosis and evaluation of severity of sepsis, monitoring inflammatory disease progress and prognostication. It has also shown potential use in liberation of ARDS patients off ventilatory support with lower IL-6 levels being associated with less frequent reintubation [63].

IL-6 has also been compared to PCT in one observational cohort study looking at 208 patients with either non-infectious SIRS, culture negative sepsis and culture positive sepsis. Culture negative and culture positive groups were compared with non-infectious SIRS groups. The most ideal IL-6 and PCT cut-offs were determined in order to differentiate one from sepsis/SIRS catagory from another. IL-6's sensitivity was 47% in the culture negative group when compared to the SIRS group while PCT 's sensitivity was 92.2% when used for the same comparison. IL-6's NPV of 41.5% was determined to be much lower than that of PCT's 82.5% NPV [64]. Therefore, a negative PCT test result is better at ruling out sepsis in the context of SIRS when the presence of infection is questioned. Other studies have similarly demonstrated that PCT is the most accurate of biomarkers in diagnosis of sepsis in this context [65–67]. However, given the often complex picture of sepsis, it is unlikely that any single biomarker will perfectly answer the question.

IL-8 is a potent 8.4 kDa chemokine and pro-inflammatory cytokine made by macrophages in order to attract neutrophils and encourage migration into inflamed tissues through promotion of adherence to the vascular wall [68]. IL-8 levels are elevated as part of the early pro-inflammatory phase in a similar manner to IL-6, before CRP is produced. Elevated IL-8 levels have been investigated for a large number of purposes. Elevated IL-8 levels have shown promise as a marker for a large variety of neoplastic and infective conditions including bladder cancer, non-Hodgkin's lymphoma, prostatitis, osteomyelitis, pulmonary infections, and acute pyelonephritis [69]. Elevated IL-8 levels—while individually not indicative of anything specific—could become more useful if combined with the collective results of other markers. For example, one retrospective case control study looking at 11 biomarkers has demonstrated a significant improvement in diagnosing ARDS in patients with severe sepsis when a five biomarker panel was used (which included both IL-8 and IL-6) [70]. Older studies have also demonstrated improved diagnostic utility of IL-8 in combination with 6 other biomarkers in diagnosing acute lung injury (ALI) [71].

Other notable biomarkers which have looked at diagnosing sepsis include two related inflammatory markers: presepsin and lipopolysaccharide binding protein (LPB). Lipopolysaccharide (LPS)-LPB complexes bind soluble CD14 (sCD14) which initiates an inflammatory cascade that can lead to SIRS. When LPS-LPB complexes bind sCD14, the N-terminus of sCD14 is cleaved off to become the 13 kDa protein presepsin [72]. In one meta-analysis looking at ten trials of 2159 cases involving either emergency or ICU patients, presepsin demonstrated a pooled sensitivity and specificity of 78 and 83%, respectively. The pooled positive likelihood ratio was 4.63 (3.27–6.55) and negative likelihood ratio 0.22 (0.16–0.30) [72]. While this meta-analysis demonstrates a moderate

diagnostic value for presepsin in the diagnosis of sepsis, there exists significant heterogeneity between studies and the cutoff values used which define a positive result in the presepsin group. In another meta-analysis and systematic review, LBP individually has also been looked at as a biomarker of sepsis. In this study—which comprised 8 prospective studies involving 1684 patients—it was shown that LBP only had a sensitivity and specificity of 64% and 63%, respectively; not particularly useful as a sole marker but perhaps useful as part of a panel [73].

Due to the complex pathophysiology of sepsis, no individual biomarker can distinguish the difference between infectious and non-infectious inflammation with 100% confidence. The future is likely to rely on panels of biomarkers which collectively produce an answer using the individual components that each biomarker represents [74]. See Table 5.6 for a complete review of other biomarkers used in sepsis.

Novel Bacterial Testing and Identification

Polymerase Chain Reaction (PCR) has traditionally been utilized as an alternative to blood cultures in selected cases of hard to identify bacterial infections. This has included non-cultivatable or slow-growing microorganisms such as mycobacteria, or certain anaerobic bacteria. Although the technique is over 20 years old, its widespread application has been limited by its cost and complexity of lab apparatus and technicians required.

In February of 2017, the US Food and Drug Administration (FDA) granted a de novo request to market the Accelerate Pheno™ system and Accelerate PhenoTest™ kit for the identification and antibiotic susceptibility testing of pathogens directly from positive blood culture samples. The de novo classification process provides a pathway intended to expedite FDA review of novel low-to-moderate risk devices for which no prior device exists. The pheno system device was determined to be of potential benefit.

The test is being promoted as way to provide rapid identification and phenotypic susceptibility to a large variety of common bacterial pathogens. The turnaround time by testing directly from positive blood culture samples is approximately 40 h faster than conventional methods [76].

The test utilizes qualitative nucleic acid fluorescence in situ hybridization (FISH) identification and quantitative antimicrobial susceptibility testing methods. It utilizes a unique morphokinetic cellular analysis (MCA) of individual microbial cells and colonies under the challenge of antibiotics. Results are intended to be interpreted in conjunction with a Gram stain results.

Although more expensive than traditional blood cultures, costs may be saved by decreasing length of stay, decreasing morbidity, and improving antibiotic stewardship.

Table 5.6 Other biomarkers used in sepsis

Sepsis (other biomarkers)									
Bio-marker	Indication	Authors	Study type	Cutoff value	Sens.	Spec.	NPV	PPV	Diagnostic Odds ratio (+ve/−ve likelihood)
PCT	Culture negative sepsis vs. SIRS	Anand et al. [64]	Prosp. Cohort study	1.43 ng/mL	92.2%	72%	82.5%	86.5%	32.09
Il-6	Culture negative sepsis vs. SIRS	Anand et al. [64]	Prosp. Cohort study	219.85 pg/mL	47%	73%	41.5%	78%	2.49
PCT	Culture positive sepsis vs. SIRS	Anand et al. [64]	Prosp. Cohort study	2.49 ng/mL	94.4%	87%	91.5%	90.5%	96.29
Il-6	Culture positive sepsis vs. SIRS	Anand et al. [64]	Prosp. Cohort study	423.5 pg/mL	63.9%	89%	88.4%	88.4%	13.5
LBP	Sepsis diagnosis	Chen et al. [73]	SR and meta-analysis	Highly variable between studies	64%	63%			3.0 (2.0–4.0)
Pre-sepsin	Sepsis diagnosis	Wu et al. [72]	SR and meta-analysis	Highly variable between studies	78%	83%			21.73 (12.81–36.86)

Conclusions

Multiple studies have demonstrated the utility of PCT measurement to guide clinical decision-making. PCT may be utilized in a wide variety of clinical scenarios to either decide to commence or withhold antibiotics; to guide the duration and possible escalation/de-escalation or to guide prognostication. The decision a clinician makes when deciding whether to withhold antibiotics in a patient depends upon the risks and benefits to primarily the patient but also to the wider healthcare system. In the case of patients with sepsis who are critically ill the risk of withholding appropriate antibiotic therapy when sepsis is suspected clinically is too great and therefore PCT is of little utility in making the decision to start antibiotics. On the other hand, in a patient with a LRTI who is considered at lower risk of bacterial infection and clinical deterioration, PCT evaluation is an evidence-based strategy to reduce unnecessary antibiotic exposure.

Once a patient is commenced on antibiotics, PCT may guide when to cease, in conjunction with a considered clinical assessment. It is noted that the IDSA guidelines for HAP/VAP currently advise using clinical criteria alone, rather than using PCT plus clinical criteria to diagnose pneumonia, but go on to give a weak recommendation for using PCT and clinical assessment to cease antibiotics [36].

The cost of any biomarker being incorporated into clinical practice is an important consideration. The NHS conducted a Health Technology Assessment and reported in 2015 that PCT algorithms reduce antibiotic exposure, do not appear to be associated with increased adverse events, and may reduce healthcare costs. This analysis found decreased hospital length of stay in both patients presenting to ED and critically ill ICU patients [75].

Most of the studies evaluating PCT are compromised by the lack of a gold standard test for sepsis. The new sepsis definitions have made progress in terms of more accurately defining hospital patients at risk of death, but they are far from the gold standard that is required to truly assess PCT as a marker of bacterial sepsis. Since PCT is produced during the "dysregulated host response" to sepsis it is not surprising that it is useful as a marker of sepsis and prognosis.

PCT is not a replacement for a thorough clinical assessment but augments the data—the clinician has to make rational decisions. It is noted that in many of the studies of PCT-guided therapy, significant numbers of included patients did not cease antibiotics when the protocol suggested, or even "mandate" cessation. Clinicians should ensure that PCT results are used in addition to the other clinical information available. Lower PCT values in viral and fungal infections may be useful in decreasing antibiotics but may falsely reassure in the case of fungal infection.

It is important that clinicians understand the confounders and limitations of PCT. PCT can be elevated in a number of conditions which induce a systemic immune response syndrome such as circulatory failure, major surgery, pancreatitis, and trauma. Also, PCT may not rise during common ICU complications such as severe localized infections including mediastinitis or abscess formation. One of the reported

strengths of PCT is the fact that it can help discriminate between patients with bacterial infections and non-bacterial/inflammatory conditions. It is important to recognize therefore that patients at risk for invasive viral or fungal infections may not mount a significantly elevated PCT despite severe infection requiring specific therapy.

Key Points

- Although sepsis guidelines recommend against the use of PCT as a diagnostic tool in sepsis, a cutoff of 0.5 mg/dL has been suggested to be a useful method of ruling out sepsis. Elevated PCT levels may also predict sepsis mortality. PCT's most promising role in sepsis is to serve as a guide to cessation of antibiotics without compromising patient safety or impacting mortality.
- PCT is quite sensitive at diagnosing bacterial pneumonia in the community and has also proven to be useful in ruling out bacterial co-infection in patients with influenza and this was especially true in ICU populations.
- Although elevations in serum PCT levels have been shown to correlate with existing indices of pneumonia severity, using these elevations to dictate level of care or antibiotics initiation should be performed with caution.
- Using PCT levels to dictate when to cease antibiotics in pneumonia is supported by the IDSA guidelines especially for ventilator-associated pneumonia. The most recent evidence points towards ceasing antibiotics at levels <0.25 μg/L. This may result in a reduction in antibiotic exposure without impacting patient outcome.
- PCT levels have been shown to be useful in diagnosing serious bacterial infections such as bacterial sepsis, meningitis, and UTI in pediatric populations.
- PCT has not been shown to be useful adjunct in the diagnosis and prognostication of sepsis in burns patients.
- PCT has some evidence in other non-infectious conditions such as pancreatitis and appendicitis as well as infectious conditions such as meningitis, infectious pulmonary effusions, bone and joint infection. PCT may also help detect bacterial infections in patients such as the immunocompromised and those with liver and kidney failure.
- PCT levels should be interpreted with caution in patients in the ICU, those receiving T-cell targeted therapy, neonates in their first two days of life and those with parenchyma tissue cancers such as small cell, medullary thyroid, and carcinoid tumors.
- Newer biomarkers have emerged and may help direct diagnosis and prognostication. Some may support existing biomarkers while others may replace them. Future translational research is required before these markers become accepted in clinical practice.

References

1. Parikh C, Koyner J. Biomarkers in acute and chronic kidney diseases. In: Skorecki K, Chertow G, Marsden P, Taal M, Yu A, editors. Brenner and rector's the kidney. 10 ed: Philadelphia: Elsevier; 2015.

2. Libby P, Gerszten RE, Ridker PM. Biomarkers, proteomics, metabolomics, and personalized medicine. In: Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. 10th ed. Philadelphia: Elsevier; 2015.
3. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–10.
4. Davies J. Procalcitonin. J Clin Pathol. 2015;68(9):675–9.
5. Sepsis Diagnostics [Internet]. Thermo Fisher Scientific. 2016. Available from: http://www.thermofisher.com/au/en/home/clinical/diagnostic-testing/condition-disease-diagnostics/infectious-disease-sepsis-diagnostics.html.
6. Povoa P, Salluh JI. Biomarker-guided antibiotic therapy in adult critically ill patients: a critical review. Ann Intensive Care. 2012;2(1):32.
7. Junker R, Schlebusch H, Luppa PB. Point-of-care testing in hospitals and primary care. Dtsch Arztebl Int. 2010;107(33):561–7.
8. Schuetz P, Kutz A, Grolimund E, Haubitz S, Demann D, Vogeli A, et al. Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: results from the randomized ProHOSP trial. Int J Cardiol. 2014;175(3):464–72.
9. Meisner M. Pathobiochemistry and clinical use of procalcitonin. Clin Chim Acta. 2002;323(1-2):17–29.
10. Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. Physiol Res. 2000;49(Suppl 1):S57–61.
11. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med. 2006;34(7):1996–2003.
12. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637.
13. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(5):426–35.
14. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. Clin Microbiol Infect. 2015;21(5):474–81.
15. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med. 2014;190(10):1102–10.
16. Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: a systematic review and meta-analysis. PLoS One. 2015;10(6):e0129450.
17. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375(9713):463–74.
18. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011;171(15):1322–31.
19. Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, et al. Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: a randomized clinical trial. JAMA Intern Med. 2016;176(9):1266–76.
20. Deliberato RO, Marra AR, Sanches PR, Martino MD, Ferreira CE, Pasternak J, et al. Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with proven bacterial infection in an intensive care setting. Diagn Microbiol Infect Dis. 2013;76(3):266–71.
21. Najafi A, Khodadadian A, Sanatkar M, Shariat Moharari R, Etezadi F, Ahmadi A, et al. The comparison of procalcitonin guidance administer antibiotics with empiric antibiotic therapy in critically ill patients admitted in intensive care unit. Acta Med Iran. 2015;53(9):562–7.
22. Oliveira CF, Botoni FA, Oliveira CR, Silva CB, Pereira HA, Serufo JC, et al. Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial. Crit Care Med. 2013;41(10):2336–43.

23. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis. 2016;16(7):819–27.
24. Berg P, Lindhardt BO. The role of procalcitonin in adult patients with community-acquired pneumonia--a systematic review. Dan Med J. 2012;59(3):A4357.
25. Schuetz P, Muller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev. 2012;(9):CD007498.
26. Morris C, Paul K, Safranek S. Procalcitonin-guided antibiotic therapy for acute respiratory infections. Am Fam Physician. 2016;94(1):53–8.
27. Ramirez P, Ferrer M, Marti V, Reyes S, Martinez R, Menendez R, et al. Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. Crit Care Med. 2011;39(10):2211–7.
28. Kruger S, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H, et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. Eur Respir J. 2008;31(2):349–55.
29. Park JH, Wee JH, Choi SP, Oh SH. The value of procalcitonin level in community-acquired pneumonia in the ED. Am J Emerg Med. 2012;30(7):1248–54.
30. Nobre V, Borges I. Nucleo Interdisciplinar de Investigacao em Medicina I. Prognostic value of procalcitonin in hospitalized patients with lower respiratory tract infections. Rev Bras Ter Intensiva. 2016;28(2):179–89.
31. Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med. 2006;174(1):84–93.
32. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA. 2009;302(10):1059–66.
33. Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis. 2012;55(5):651–62.
34. Schuetz P, Muller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Evid Based Child Health. 2013;8(4):1297–371.
35. Li H, Luo YF, Blackwell TS, Xie CM. Meta-analysis and systematic review of procalcitonin-guided therapy in respiratory tract infections. Antimicrob Agents Chemother. 2011;55(12):5900–6.
36. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–e111.
37. Stolz D, Smyrnios N, Eggimann P, Pargger H, Thakkar N, Siegemund M, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J. 2009;34(6):1364–75.
38. Luyt CE, Guerin V, Combes A, Trouillet JL, Ayed SB, Bernard M, et al. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. Am J Respir Crit Care Med. 2005;171(1):48–53.
39. Wu MH, Lin CC, Huang SL, Shih HM, Wang CC, Lee CC, et al. Can procalcitonin tests aid in identifying bacterial infections associated with influenza pneumonia? A systematic review and meta-analysis. Influenza Other Respir Viruses. 2013;7(3):349–55.
40. Long W, Li LJ, Huang GZ, Zhang XM, Zhang YC, Tang JG, et al. Procalcitonin guidance for reduction of antibiotic use in patients hospitalized with severe acute exacerbations of asthma: a randomized controlled study with 12-month follow-up. Crit Care. 2014;18(5):471.
41. Tang J, Long W, Yan L, Zhang Y, Xie J, Lu G, et al. Procalcitonin guided antibiotic therapy of acute exacerbations of asthma: a randomized controlled trial. BMC Infect Dis. 2013;13:596.

42. Ding J, Chen Z, Feng K. Procalcitonin-guided antibiotic use in acute exacerbations of idiopathic pulmonary fibrosis. Int J Med Sci. 2013;10(7):903–7.
43. Ogasawara T, Umezawa H, Naito Y, Takeuchi T, Kato S, Yano T, et al. Procalcitonin-guided antibiotic therapy in aspiration pneumonia and an assessment of the continuation of oral intake. Respir Investig. 2014;52(2):107–13.
44. Maisel A, Neath SX, Landsberg J, Mueller C, Nowak RM, Peacock WF, et al. Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial. Eur J Heart Fail. 2012;14(3):278–86.
45. Ren H, Li Y, Han C, Hu H. Serum procalcitonin as a diagnostic biomarker for sepsis in burned patients: a meta-analysis. Burns. 2015;41(3):502–9.
46. Mann EA, Wood GL, Wade CE. Use of procalcitonin for the detection of sepsis in the critically ill burn patient: a systematic review of the literature. Burns. 2011;37(4):549–58.
47. Yu CW, Juan LI, Hsu SC, Chen CK, Wu CW, Lee CC, et al. Role of procalcitonin in the diagnosis of infective endocarditis: a meta-analysis. Am J Emerg Med. 2013;31(6):935–41.
48. Mofidi R, Suttie SA, Patil PV, Ogston S, Parks RW. The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. Surgery. 2009;146(1):72–81.
49. Wu JY, Lee SH, Shen CJ, Hsieh YC, Yo PH, Cheng HY, et al. Use of serum procalcitonin to detect bacterial infection in patients with autoimmune diseases: a systematic review and meta-analysis. Arthritis Rheum. 2012;64(9):3034–42.
50. Shen CJ, Wu MS, Lin KH, Lin WL, Chen HC, Wu JY, et al. The use of procalcitonin in the diagnosis of bone and joint infection: a systemic review and meta-analysis. Eur J Clin Microbiol Infect Dis. 2013;32(6):807–14.
51. Zou MX, Zhou RR, Wu WJ, Zhang NJ, Liu WE, Fan XG. The use of pleural fluid procalcitonin and C-reactive protein in the diagnosis of parapneumonic pleural effusions: a systemic review and meta-analysis. Am J Emerg Med. 2012;30(9):1907–14.
52. Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg. 2013;100(3):322–9.
53. Henry BM, Roy J, Ramakrishnan PK, Vikse J, Tomaszewski KA, Walocha JA. Procalcitonin as a serum biomarker for differentiation of bacterial meningitis from viral meningitis in children: evidence from a meta-analysis. Clin Pediatr (Phila). 2016;55(8):749–64.
54. Vikse J, Henry BM, Roy J, Ramakrishnan PK, Tomaszewski KA, Walocha JA. The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis. Int J Infect Dis. 2015;38:68–76.
55. Wei TT, Hu ZD, Qin BD, Ma N, Tang QQ, Wang LL, et al. Diagnostic accuracy of procalcitonin in bacterial meningitis versus nonbacterial meningitis: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(11):e3079.
56. Lin K, Wang F, Wu M, Jiang B, Kao W, Chao H, Wu J, Lee C. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection in patients with liver cirrhosis: a systematic review and meta-analysis. Diagnostic Microbiology and Infectious Disease, 2014;80(1):pp.72–78.
57. Lu XL, Xiao ZH, Yang MY, Zhu YM. Diagnostic value of serum procalcitonin in patients with chronic renal insufficiency: a systematic review and meta-analysis. Nephrol Dial Transplant. 2013;28(1):122–9.
58. Schaper F, Rose-John S. Interleukin-6: biology, signaling and strategies of blockade. Cytokine Growth Factor Rev. 2015;26(5):475–87.
59. Wirtz DC, Heller KD, Miltner O, Zilkens KW, Wolff JM. Interleukin-6: a potential inflammatory marker after total joint replacement. Int Orthop. 2000;24(4):194–6.
60. Marino A, Giotta N. Cinacalcet, fetuin-a and interleukin-6. Nephrol Dial Transplant. 2008;23(4):1460–1. Author reply 1–2
61. Zant R, Melter M, Knoppke B, Ameres M, Kunkel J. Kinetics of interleukin-6, procalcitonin, and C-reactive protein after pediatric liver transplantation. Transplant Proc. 2014;46(10):3507–10.

62. Calandra T, Gerain J, Heumann D, Baumgartner JD, Glauser MP. High circulating levels of interleukin-6 in patients with septic shock: evolution during sepsis, prognostic value, and interplay with other cytokines. The Swiss-Dutch J5 Immunoglobulin Study Group. Am J Med. 1991;91(1):23–9.
63. Alladina JW, Levy SD, Hibbert KA, Januzzi JL, Harris RS, Matthay MA, et al. Plasma concentrations of soluble suppression of tumorigenicity-2 and interleukin-6 are predictive of successful liberation from mechanical ventilation in patients with the acute respiratory distress syndrome. Crit Care Med. 2016;44(9):1735–43.
64. Anand D, Das S, Bhargava S, Srivastava LM, Garg A, Tyagi N, et al. Procalcitonin as a rapid diagnostic biomarker to differentiate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: a prospective, observational, cohort study. J Crit Care. 2015;30(1):218.e7–12.
65. Ruiz-Alvarez MJ, Garcia-Valdecasas S, De Pablo R, Sanchez Garcia M, Coca C, Groeneveld TW, et al. Diagnostic efficacy and prognostic value of serum procalcitonin concentration in patients with suspected sepsis. J Intensive Care Med. 2009;24(1):63–71.
66. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med. 2001;164(3):396–402.
67. Mat-Nor MB, Md Ralib A, Abdulah NZ, Pickering JW. The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality. J Crit Care. 2016;33:245–51.
68. Dong R, Zheng S. Interleukin-8: a critical chemokine in biliary atresia. J Gastroenterol Hepatol. 2015;30(6):970–6.
69. Shahzad A, Knapp M, Lang I, Kohler G. Interleukin 8 (IL-8)—a universal biomarker? Int Arch Med. 2010;3:11.
70. Ware LB, Koyama T, Zhao Z, Janz DR, Wickersham N, Bernard GR, et al. Biomarkers of lung epithelial injury and inflammation distinguish severe sepsis patients with acute respiratory distress syndrome. Crit Care. 2013;17(5):R253.
71. Fremont RD, Koyama T, Calfee CS, Wu W, Dossett LA, Bossert FR, et al. Acute lung injury in patients with traumatic injuries: utility of a panel of biomarkers for diagnosis and pathogenesis. J Trauma. 2010;68(5):1121–7.
72. Wu J, Hu L, Zhang G, Wu F, He T. Accuracy of presepsin in sepsis diagnosis: a systematic review and meta-analysis. PLoS One. 2015;10(7):e0133057.
73. Chen KF, Chaou CH, Jiang JY, Yu HW, Meng YH, Tang WC, et al. Diagnostic accuracy of lipopolysaccharide-binding protein as biomarker for sepsis in adult patients: a systematic review and meta-analysis. PLoS One. 2016;11(4):e0153188.
74. Biron BM, Ayala A, Lomas-Neira JL. Biomarkers for sepsis: what is and what might be? Biomark Insights. 2015;10(Suppl 4):7–17.
75. Westwood M, Ramaekers B, Whiting P, Tomini F, Joore M, Armstrong N, et al. Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2015;19(96):v–xxv, 1–236.
76. FDA allows marketing of test to identify organisms that cause bloodstream infections and provide antibiotic sensitivity results. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm543150.htm. Accessed 5 Mar 2017.

Chapter 6
New Developments and Treatment Options of Cellulitis in the Hospital

Stephanie Bender and Katherine Oakden

Introduction

Cellulitis is an infection of the skin and adjacent subcutaneous tissues, characterized by spreading erythema, edema, warmth, and tenderness. It is a common problem encountered in both the ambulatory and inpatient setting. In the United States, an estimated 14.5 million cases annually of cellulitis account for $3.7 billion in ambulatory care costs alone. Furthermore, a significant proportion of patients with cellulitis are hospitalized for management, and inpatient numbers are increasing. The number of hospital stays for cellulitis or abscess in the United States has risen by 73%, from 12 per 10,000 in 1997 to 21 per 10,000 in 2011.

Along with a rising incidence of cellulitis, is an increase in readmission rates from misdiagnosis of the condition. It is estimated that with more than 650,000 admissions per year in the US alone, misdiagnosis rates are as high as 33%, ultimately resulting in high ED readmission rates. In one subgroup of hospitalized patients with cellulitis who required dermatology consultation, the misdiagnosis rate was 74% [5]. A cross-sectional study using patients admitted from the emergency department [ED] of a large urban hospital with a diagnosis of lower extremity cellulitis between June 2010 and December 2012 found an estimated cellulitis misdiagnosis leads to 50,000 to 130,000 unnecessary hospitalizations and $195 million to $515 million in avoidable health care spending. Unnecessary antibiotics and hospitalization for misdiagnosed cellulitis are projected to cause more than 9000 nosocomial

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infections, 1000 to 5000 Clostridium difficile infections, and 2 to 6 cases of anaphylaxis annually [4]. Structured guidelines on diagnosis and proper treatment of cellulitis can help minimize these readmission rates and cut back on healthcare spending.

Pathophysiology

Cellulitis is a deep dermal and subcutaneous infection that occurs when pathogens gain entry into the dermis through breaks in the skin. This cutaneous barrier disruption can be caused by toe web space bacteria, fungal foot infections [e.g., tinea pedis, onychomycosis], pressure ulcers, and venous leg ulcers, among other causes. Portal of entry is apparent in most patients, with nearly half being caused by superficial fungal infection, usually tinea pedis with or without concomitant onychomycosis. The majority of cases are nonculturable and therefore the causative bacteria are unknown. Cellulitis in immunocompetent adults is usually thought to be caused by group A streptococci [*Streptococcus pyogenes*], with *Staphylococcus aureus* as a notable, but less common cause. However, given the difficulty culturing cellulitis, the specific causative bacterium in most cases remains unknown, and several studies demonstrate conflicting evidence in regard to prevalence of causative organisms [1].

Purulent cellulitis encompasses either a process that began as an abscess and resulted in secondary cellulitis or as a cellulitis with secondary purulence, purulent drainage, or exudate in the absence of a drainable abscess [1, 2, 6]. Presence of a purulent process makes infection with *S aureus* more likely. In fact, the 2011 Infectious Disease Society of America clinical practice guidelines use the description of purulence to define MRSA cellulitis [1]. MRSA should be considered for purulent infections in known high-risk populations, such as athletes, children, men who have sex with men, prisoners, military recruits, residents of long-term care facilities, individuals with previous MRSA exposure, and intravenous drug users [1].

Less common causes of cellulitis are usually implicated in special clinical circumstances. Patients presenting with particular comorbidities or in certain clinical contexts should alert clinicians to consider uncommon organisms. Immunosuppression, kidney disease, liver disease, bites, and aquatic injuries carry increased risks for particular pathogenic organisms. Regardless of circumstances, *S aureus* and GAS must be suspected in all patients with cellulitis [1, 6].

Presentation

Cellulitis usually presents as an acute, spreading, and poorly demarcated area of erythema. The skin findings in cellulitis follow the classic signs of inflammation: dolor [pain], calor [heat], rubor [erythema], and tumor [swelling]. It spreads

proximally from portal of entry as an expanding solitary lesion. Vesicles, bullae, and abscesses may form in the plaque. Additional clinical features may include dilated and edematous skin lymphatics, leading to a peau d'orange [orange peel] appearance; bulla formation; or inflamed lymphatics proximal to the area of cellulitis, leading to linear erythematous streaks or lymphangitis. Inflammation in the lymphatics may also result in regional tender lymphadenopathy [1, 3].

Cellulitis is nearly always unilateral. It is typically found on the lower extremities, although it can appear on any area of the skin and is often found on the upper extremities in patients who are intravenous drug users [1, 3]. The presence of fever is variable.

It is important to note whether the infection is purulent or nonpurulent as this affects the course of treatment. Abscesses and cellulitis can coexist within the same patient and can lead to treatment failure if source control is not achieved. The distinction between cellulitis and abscess can often be made on physical exam. Ultrasound, either bedside or per radiology, is increasingly being used to determine the extent of abscess formation [1, 6].

Risk Factors

Systemic and local risk factors are associated with the development of primary and recurrent cellulitis. The most common risk factor for cellulitis is edema, especially lymphedema, as it is thought to facilitate bacterial growth [1]. Local risk factors include barrier disruption [wounds, ulcers, trauma], toe web infection, tinea pedis, prior history of cellulitis, history of skin disease [i.e., psoriasis, atopic dermatitis], venous insufficiency, xerosis, dermatitis, prior saphenous venectomy, prior ipsilateral surgical procedure, and prior breast conservation surgery [1, 3].

Differential Diagnosis

The clinical tetrad of dolor, calor, rubor, and tumor was actually first ascribed to inflammation rather than infection. Thus there are many conditions which generate cutaneous inflammation and clinically mimic cellulitis that fall under the umbrella term, pseudocellulitis. These can also induce fever, malaise and leukocytosis, further confusing the clinical picture between cellulitis and pseudocellulitis. Distinguishing one from the other may be challenging [1, 5] and can lead to high rates of misdiagnosis, as mentioned earlier.

Multiple noninfectious, nonnecrotizing, inflammatory conditions of the dermis or subcutis can mimic cellulitis, with stasis dermatitis as the most common. It is primarily distinguished by its bilateral nature because bilateral cellulitis in the absence of trauma is rare. However, unilateral presentations of stasis dermatitis can occur, particularly with a history of unilateral leg injury or anatomical variations,

such as varicosities. Another common condition mistaken for cellulitis is a hematoma. Hematomas are often found in patients on anticoagulation medication and with a history of trauma. The appropriate diagnosis can be confirmed with ultrasound. Lastly, gout presenting with fever and leukocytosis can closely resemble cellulitis. It should be included as a differential in patient presentations where erythema overlies a joint. To differentiate one from another, blood work including uric acid levels, a trial with NSAIDs or steroids, and joint aspiration may be appropriate.

There are less common conditions that imitate cellulitis that must be recognized differentiated early, as they are potentially life threatening and appropriate treatment needs be initiated quickly. These include erythema migrans, calciphylaxis, and necrotizing fasciitis. The majority of cases of erythema migrans [EM] present with self-resolving, homogenous erythema, not the classic annular lesion, and leads to adverse sequelae if left untreated. EM is well demarcated whereas cellulitis is poorly demarcated. Early lesions of calciphylaxis present analogously to cellulitis, although patients typically have severe pain out of proportion to physical examination findings and the pain is greater in intensity than that routinely observed with cellulitis. Calciphylaxis should be considered in these cases, particularly in at-risk populations such as patients with end-stage renal disease, diabetes, obesity, liver disease, or those receiving warfarin [1, 3].

Necrotizing Fasciitis

Necrotizing fasciitis is a rapidly progressive infection of subcutaneous tissue with a high mortality rate. It may initially resemble cellulitis with spreading erythema; however, the skin may initially be spared. It also presents with pain out of proportion to clinical findings, edema, necrosis, bullae, cutaneous numbness, fever, and crepitus. It is important to recognize early because prompt surgical intervention is required.

Failure to respond to appropriate therapy or multiple, symmetric, long-standing or slowly progressive lesions along with the presence of certain physical examination findings should prompt a consideration of other diagnoses. Pain in the absence of erythema; pain out of proportion to the appearance of the local area; crepitus, a rare sign that signifies gas-forming pathogens; and macular erythema followed by diffuse epidermal exfoliation should raise concern for staphylococcal scalded skin syndrome [6].

Diagnosis

Diagnosis is clinical and based on history [trauma, exposures, bites] as well as on the appearance of the skin. Clinicians should look for a red, warm, edematous plaque which has spread from a portal of entry which is usually apparent. The focus

should include the lower legs, as they are the most common site of infection [3]. It is often tender and painful with irregular, raised borders and significant confluent edema surrounding the area. Vesicles, bullae, abscesses, and erosions may form in the plaque. Lymphangitis and tender lymphadenopathy may be present.

Unfortunately, there are no gold standard diagnostic techniques to confirm the diagnosis of cellulitis, as the indicators that are elevated in cellulitis are nonspecific for said disease. These include an increased white count, ESR, and CRP [1]. Routine and uncomplicated cellulitis in patients without comorbidities or complications [fever, diabetes, immunosuppression] does not require lab testing. The presence of accompanied systemic signs [fever, tachycardia above 100 beats/minute, and hypotension with systolic pressure less than 90 mmHg] classifies the infection as complicated cellulitis and further workup, including cultures, is warranted [10].

Indications for Culture

Cultures in mild cellulitis are of limited benefit. Most cases of cellulitis are nonculturable and those performed with needle aspiration and biopsy usually yield negative results. Therefore, cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended. If the infection is associated with purulence, a gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is still reasonable in typical cases. Patients who are at increased risk for complicated cellulitis or have abnormal exposure history [malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, bites, chronic liver disease, chronic kidney disease, aquatic injury] should be considered for blood cultures, and cultures and microscopic examination of cutaneous aspirates, punch biopsies or swabs [1, 2].

Skin surface swab cultures of chronic wounds and ulcers are commonly polymicrobial or colonized with MDR pathogens that are not involved in the etiology of the underlying cellulitis. The Infectious Disease Society of America does not recommend routine swab cultures in the management of infected ulcers [1].

Ultimately, the 2014 Infectious Disease Society of America guidelines recommend against performing routine blood, skin aspirate, swab, or biopsy cultures. Instead, blood cultures are strongly recommended and tissue cultures are recommended only for patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites [1, 2].

Imaging

Imaging studies are not diagnostic, but can help distinguish cellulitis from more severe forms of infection. They can also identify any drainable fluid collections, such as abscesses. For identification of drainable pus collections, the most widely

used modalities are ultrasound or MRI. Ultrasound detects occult abscesses, which can help prevent unnecessary invasive procedures and provide guidance for further imaging [1]. Point of care ultrasound in the ER is used to diagnose an occult abscess, determine the safest route for abscess incision or drainage, and avoid complications during abscess evacuation in either a static or dynamic manner [7]. Osteomyelitis can complicate cellulitis and when suspected should be ruled out with MRI. MRI and CT can also help differentiate cellulitis from necrotizing fasciitis and pyomyositis, thus preventing misdiagnosis [1].

Consult

If the diagnosis of cellulitis is unclear or there is concern for other serious conditions such as necrotizing fasciitis, dermatology consult should be considered in hospitalized patients. Involving dermatologists may improve diagnostic accuracy and decrease unnecessary antibiotic use. [5]

Approach to Treatment

As discussed previously, cellulitis involves the deeper dermis and subcutaneous fat and is most commonly implicated by *Staphylococcus aureus* and GAS. It can be divided into non-purulent and purulent cellulitis and treatment is based on extent of infection and risk factors [6]. Outpatient therapy is recommended for patients who do not have SIRS, altered mental status, or hemodynamic instability. Hospitalization is additionally recommended if there is concern for a deeper or necrotizing infection, for patients with poor adherence to therapy, for infection in a severely immunocompromised patient, or if outpatient treatment is failing [2].

In general, treatment durations for outpatient cellulitis range from 5 to 10 days. Immunocompromised patients may require 7–14 days [1, 2]. Patient and clinician reassessment of the clinically affected area for improvement in pain, redness, swelling, or warmth should occur within 24–48 h of treatment initiation. If unimproved or worsened, adjustment of antibiotic selection should be considered for possible resistant pathogens such as MRSA or alternative diagnoses should be sought [1].

Despite published guidelines, little evidenced-based agreement exists on a preferred antibiotic approach to cellulitis. A Cochrane review of 25 randomized controlled clinical studies on the diagnosis and management of cellulitis could not provide treatment recommendations because no two studies used the same treatment regimen [1, 4]. In general, antibiotic selection is guided by commonly suspected pathogens.

Nonpurulent Cellulitis: Antibiotic Choices

In most cases of nonpurulent and uncomplicated cellulitis, narrow spectrum antibiotics against *streptococcus* and methicillin-sensitive *Staphylococcus aureus* remain appropriate [1]. These include cephalexin, dicloxacillin, amoxicillin/clavulanate or in cases of PCN allergy, the use of clindamycin [1, 2]. The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period [2].

The presence of systemic signs of infection associated with cellulitis infections has been shown to predict failure of empirical outpatient antibiotic therapy; therefore, broad spectrum antibiotics are indicated in these cases. Patients who meet only one SIRS criteria can still initially receive oral agents for mild cellulitis. However, patients who meet 2 or more SIRS criteria or who fail oral agents should be considered for an intravenous regimen of cefazolin, ceftriaxone, or, in cases of penicillin allergy, clindamycin. For patients whose cellulitis is severe with associated penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, or history of injection drug use; vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended.

In severely immunocompromised patients, broad-spectrum antimicrobial coverage may also be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections [2]. Oral linezolid is an alternative to vancomycin in patients who cannot receive or have a contraindication to intravenous vancomycin. Clindamycin, linezolid, daptomycin, or ceftaroline are also options [1, 2].

Purulent Cellulitis: Antibiotic Choices

Although gram stain and culture of pus from carbuncles and abscesses is recommended by the Infectious Disease Society of America, treatment without these studies is reasonable in typical cases. For purulent cellulitis without systemic signs of infection [mild cellulitis] and no suspicion for MRSA infection; cephalexin, dicloxacillin, amoxicillin/clavulanate, or, in cases of penicillin allergy, clindamycin should be considered [1]. If MRSA is suspected in these mild purulent cases, trimethoprim-sulfamethoxazole, doxycycline, or minocycline should be used. These agents, however, do not offer adequate streptococcal coverage, and cephalexin or penicillin should be added if culture reveals that both organisms are involved. Clindamycin or linezolid is an option for penicillin-allergic patients. An antibiotic active against MRSA is also recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or who have markedly impaired host defenses or in patients with SIRS and hypotension [2].

Patients with purulent cellulitis that meet a single criterion for SIRS [moderate cellulitis] can be initially treated with the same oral agents effective for mild disease. Patients who meet two or more criteria for SIRS should be considered for intravenous antibiotics such as oxacillin, nafcillin, or cefazolin for suspected methicillin-sensitive *S aureus*, or vancomycin, clindamycin, or linezolid for suspected MRSA [1].

A 2013 Cochrane review comparing oral linezolid with intravenous vancomycin for the treatment of skin and soft tissue infections demonstrated that linezolid had better clinical and microbiological cure rates overall [RR, 1.09 vs 1.08; 95% CI, 1.03–1.16 vs 1.01–1.16, respectively], as well as for MRSA infections [relative risk [RR], 1.09 vs 1.17; 95% CI, 1.03–1.17 vs 1.04–1.32, respectively], with a 3-day-shorter length of stay, leading to overall reduced costs despite linezolid use being more expensive [12]. However, prescribing clinicians should be aware of the increased cost, increased incidence of serotonin syndrome in patients concomitantly receiving a serotonergic agent [0.24–4%], and increased risk of thrombocytopenia with long-term use [RR, 13.06; 95% CI, 1.72–99.22] [1, 8].

In addition to antibiotic therapy, incision and drainage is the recommended treatment for carbuncles and abscesses and large furuncles.

For all cases of purulent cellulitis, coverage should be narrowed according to culture results [if available], response after 24–48 h, and given risk factors. If symptoms are unresponsive after 24–48 h, possible pseudocellulitis or resistant or atypical organisms should be considered. In immunocompromised patients, numerous organisms can cause cellulitis, and broader antimicrobial coverage should be considered for fungal, viral, and parasitic organisms in addition to bacteria. Early biopsy or aspiration for histologic and microbiological review should be conducted [1].

Treatment of Recurrent Cellulitis

When recurrent disease occurs, identification and treatment of predisposing conditions such as edema, obesity, eczema, venous insufficiency, and toe web space abnormalities should be pursued to help prevent repeated infections [1, 2]. Regular foot examinations; dry skin care; treatment of tinea pedis, onychomycosis, or other chronic dermatoses; use of support hose and other tools for lymphedema control; and intensive wound care for ulceration can help prevent primary and recurrent cellulitis [1]. These practices should be performed as part of routine patient care and certainly during the acute stage of cellulitis [2].

Administration of prophylactic antibiotics, such as oral penicillin or erythromycin bid for 4–52 weeks, or intramuscular benzathine penicillin every 2–4 weeks, should be considered in patients who have 3–4 episodes of cellulitis per year despite attempts to treat or control predisposing factors. This program should be continued so long as the predisposing factors persist [2].

Additional Therapy

Elevation of the affected area and treatment of predisposing factors, such as edema or underlying cutaneous disorders, are recommended [2]. Addressing predisposing factors can also minimize risk of recurrence [1]. In lower-extremity cellulitis, clinicians should carefully examine the interdigital toe spaces because treating fissuring, scaling, or maceration may eradicate colonization with pathogens and reduce the incidence of recurrent infection [2]. For patients with recurrent MRSA skin infections, topical antibiotics such as mupirocin have been prescribed to decolonize carriers of the bacteria to reduce further infections [11]. Trials have demonstrated that the use of intranasal mupirocin along with an antimicrobial body wash such as chlorhexidine has significantly reduced the number of recurrent staphylococcal skin infections; however, there is concern for the development of antibiotic resistance in the near future [11].

New Emerging Treatments

The high cost of lengthy treatments for skin infections has driven research towards finding new treatments. Tedizolid, a novel oxazolidinone with gram-positive activity including MRSA, is promising because it can be administered daily in oral or intravenous forms [6, 13, 14]. The lipoglycopeptide class of antibiotics [telavancin, dalbavancin, and oritavancin] have recently been introduced as options to treat skin and soft tissue infections, including MRSA cellulitis, with some requiring less frequent dosing than typical antibiotics [6, 13, 14]. Telavancin has been evaluated in several trials and has been shown to be noninferior to vancomycin with less frequent dosing [14].

However, prescribing clinicians should be aware of the observed renal dysfunction that occurs with telavancin and should use with caution in patients with previous renal conditions [14]. Dalbavancin, a second-generation lipoglycopeptide that covers MRSA, can be administered as infrequently as once weekly [13, 14]. This once weekly dalbavancin has been shown to be noninferior to a course of twice daily IV vancomycin followed by oral linezolid in two double-blinded randomized controlled trials [9]. Oritavancin has proven to be the most novel of the lipoglycopeptides with a trial that has shown that a single dose is as effective as twice-daily intravenous vancomycin [9]. In this randomized double blind trial, 475 patients received one dose of 1200 mg of oritavancin and 479 patients received IV vancomycin twice a day for seven to 10 days; all for treatment of an acute bacterial skin infection. Clinical cure was achieved in 79.6% of oritavancin participants versus 80.0% in the vancomycin group [9]. These new emerging treatments have the potential to increase patient adherence to treatment and decrease healthcare spending associated with high readmission rates and lengthy hospital stays.

Key Points

- Cellulitis is a common problem in the United States and there is a rising incidence in hospital readmission rates from misdiagnosis. Guidelines on diagnosis and treatment of cellulitis can help reduce readmissions and cut down on healthcare spending.
- The clinical presentation and its similarities to other common conditions make misdiagnosis fairly common. Stasis dermatitis is the most common mimic of cellulitis as it also presents as a poorly demarcated area of erythema; however, it is usually bilateral in nature. Other common differentials include hematoma and gout. Necrotizing fasciitis also has a similar presentation and must be recognized immediately as it has a high mortality rate.
- Antibiotic selection can be determined by the presence of purulence. Non-purulent cellulitis can be treated with narrow spectrum antibiotics against streptococcus and methicillin sensitive *Staphylococcus aureus*. In cases of purulent cellulitis, MRSA should be suspected and antibiotic coverage should account for it.
- Systemic signs have been shown to predict outpatient failure and in these cases, broad spectrum antibiotics should be used. If only one SIRS criteria is present, oral antibiotics can still be used. If two or more SIRS criteria is met, intravenous antibiotics should be considered,
- New emerging treatments have been developed to help increase patient compliance. The lipoglycopeptide class of antibiotics have been shown to be non-inferior to present treatment yet require less dosing. Oritavancin has been shown to be effective for cellulitis infections with just a single dose.

References

1. Stevens DL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10–52.
2. Eljaaly K, et al. Antibiotic dosing discrepancies in the 2014 skin and soft tissue infections guidelines. Clin Infect Dis. 2015;60(11):1731–2.
3. Wolff K, Johnson RA, Saavedra AP. Fitzpatricks color atlas and synopsis of clinical dermatology. 7th ed. New York: McGraw-Hill; 2013. p. 531–41.
4. Raff AB, Kroshinsky D. Cellulitis: a review. JAMA. 2016;316(3):325–37.
5. Moran GJ, et al. Acute bacterial skin infections: developments since the 2005 Infectious Diseases Society of America (IDSA) guidelines. J Emerg Med. 44(6):e397–412.
6. Miller LG, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. NEJM. 2015;372(12):1093–103.
7. Chen KC, et al. An overview of point-of-care ultrasound for soft tissue and musculoskeletal applications in the emergency department. Journal of intensive care. 2016;4:55.
8. Ibrahim F, Khan T, Pujalte GG. Bacterial skin infections. Prim Care. 2015;42(4):485–99. doi:10.1016/j.pop.2015.08.001. Review.

9. Corey GR, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med. 2014;370(23):2180–90.
10. Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother. 2010;65(Suppl 3):iii35–44.
11. Creech CB, Al-Zubeidi DN, Fritz SA. Prevention of recurrent staphylococcal skin infections. Infect Dis Clin N Am. 2015;29(3):429–64.
12. Yue J, Dong B R, Yang M, Chen X, Wu T. & Liu G. J. Linezolid versus vancomycin for skin and soft tissue infections. Evidence-Based Child Health: A Cochrane Review Journal. 2014;9(1):103–66.
13. Prokocimer P, De Anda C, Fang E, Mehra P, & Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. Jama. 2013;309(6):559–69.
14. Pulia, M. S., Calderone, M. R., Meister, J. R., Santistevan, J., & May, L. Update on management of skin and soft tissue infections in the emergency department. Current infectious disease reports. 2014;16(9):418.

Chapter 7
An In-depth Look into the Management and Treatment of Delirium

Scott M. Fiedler and David J. Houghton

Introduction

Delirium is defined as an acute confusional state, exemplified by fluctuating alterations in mental status, attention, and cognition. Delirium develops in predisposed people with underlying conditions or precipitated by insults [1] (Table 7.1). Delirium can be conceptualized as an acute brain failure, analogous to an acute kidney injury or acute heart failure, whereas dementia can be thought of as chronic brain failure, similar to CHF or COPD [2]. The development of delirium signals poor cognitive reserve and may not be as reversible as previously thought [2, 3]. A growing amount of evidence suggests an incident of delirium may cause permanent cognitive damage and accelerated cognitive decline, analogous to acute heart failure leading to CHF [2–4].

Delirium Subtypes

Delirium can be broken down into four distinct subtypes based on clinical features. These four subtypes include hypoactive, hyperactive, mixed, and subsyndromal delirium. Hypoactive delirium is typically found more commonly in

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Table 7.1 Assessment and management of suspected delirium

Assessment	Actions
History	Check baseline cognitive function and recent (within past 2 weeks) changes in mental status (e.g., family, staff)
	Recent changes in disorder, new diagnoses, complete review of systems
	Review all current drugs (including over-the-counter and herbal preparations); pay special attention to new drugs and drug interactions
	Review alcohol and sedative use
	Assess for pain and discomfort (e.g., urinary retention, constipation, thirst)
Vital signs	Measure temperature, oxygen saturation, fingerstick glucose concentration
	Take postural vital signs as needed
Physical and neurological examination	Search for signs of occult infection, dehydration, acute abdominal pain, deep vein thrombosis, other acute illness; assess for sensory impairments
	Search for focal neurological changes and meningeal signs
Targeted laboratory assessment (selected tests based on clues from history and physical)[a]	Consider full blood count; urinalysis; measurement of concentrations of electrolytes, calcium, and glucose; measurement of renal, liver, and thyroid function; taking cultures of urine, blood, sputum; measurement of drug concentrations; measurement of concentrations of ammonia, vitamin B12, and cortisol measure arterial blood gas
	Do electrocardiography
	Chest radiography
	Lumbar puncture should be reserved for assessment of fever with headache and meningeal signs or suspicion of encephalitis
Targeted neuroimaging (selected patients)	Assess focal neurological changes (stroke can present as delirium)
	Test for suspected encephalitis (for temporal lobe changes)
	Assess patients with histories or signs of head trauma
Electroencephalography (selected patients)	Assess for occult seizures
	Differentiate psychiatric disorder from delirium
Management	
Drug adjustments	Reduce or remove psychoactive drugs (e.g., anticholinergics, sedatives or hypnotics, opioids); lower dosages; avoid as required dosing
	Substitute less toxic alternatives
	Use non-pharmacological approaches for sleep and anxiety, including music, massage, relaxation techniques
Address acute medical issues	Treat problems identified in work-up (e.g., infection, metabolic disorders)
	Maintain hydration and nutrition
	Treat hypoxia

(continued)

Table 7.1 (continued)

Assessment	Actions
Reorientation strategies	Encourage family involvement; use companions as needed
	Address sensory impairment; provide eyeglasses, hearing aids, interpreters
Maintain safe mobility	Avoid use of physical restraints, tethers, and bed alarms
	Ambulate patient at least three times per day; active range-of-motion
	Encourage self-care and regular communication
Normalize sleep–wake cycle	Discourage napping and encourage exposure to bright light during the day
	Try to provide uninterrupted period for sleep at night
	Provide non-pharmacological sleep protocol and quiet room at night with low level lighting
Pharmacological management	Reserve for patients with severe agitation that interrupts essential treatment (e.g., intubation) or severe psychotic symptoms
	Consider low dose neuroleptics and titrate until effect achieved

[a]Not all of these tests should be done in all patients; rather, specific tests should be guided by history, physical examination, and previous results

hospice and palliative care patients and is associated with the worst outcomes [2, 5, 6]. Hyperactive delirium is characterized by significant agitation and is the easiest to recognize among the delirium subtypes [7]. Mixed delirium fluctuates between hyperactive and hypoactive subtypes and is the most commonly diagnosed type of delirium [6]. Lastly, subsyndromal delirium is characterized as having persistent delirium symptoms yet failing to meet diagnostic criteria for delirium [8].

Features of hypoactive delirium include poor concentration, slowed responses or speech, decreased mobility, decreased movements, lethargy, apathy, and withdrawal [6, 9]. In addition to the difficult nature of recognizing features of hypoactive delirium, many of the symptoms can be readily attributed to other causes (e.g., feature of disease condition, severe fatigue, preexisting dementia, medications, depression), resulting in under recognition and non-detection rates ranging from 33 to 66% [6–8, 10–14]. Additionally, differentiating delirium from depression requires collateral history from family or caretakers. Delirium is characterized by an acute onset, whereas depressive symptoms must be present for weeks to reach diagnostic criteria. Depressive symptoms such as low mood, anhedonia, feelings of worthlessness, and suicidal ideation were found in more than half of delirium patients in one study and cannot be reliably used to differentiate the two conditions [10]. However, one study found disorientation to time (OR 4.4, 95% CI 1.7–11.1) and place (OR 3.8, 95% CI 1.7–8.2) at admission correctly identified delirium at inpatient follow-up in over 88% of subjects [15]. Moreover, the most commonly used instruments to

assess delirium severity have a larger proportion of hyperactive symptoms in their cumulative scores; solely relying on a single measure, such as the confusion assessment method (CAM), may result in missed cases of hypoactive delirium [2, 6, 16]. In light of the symptomatology of hypoactive delirium, patients are more likely to experience decubitus ulcers and nosocomial infections. Studies also show hypoactive delirium is associated with metabolic disorders, organ failure, and benzodiazepines [12]. These associations provide a likely explanation for why hypoactive delirium is more commonly found in hospice and palliative care settings with a prevalence ranging from 20 to 83% [6, 12]. Hypoactive delirium is also more common in the elderly and is associated with the poorest outcomes [2, 5].

Conversely, hyperactive delirium is the "classic" picture of delirium characterized by significant agitation, sympathetic arousal, hypervigilance, restlessness, attempts to remove lines and catheters, irritability, combativeness, wandering, distractibility, and tangentiality [6–8]. As a result, these patients are more likely to experience falls compared to other subtypes of delirium. The demographics for hyperactive delirium also differs from their hypoactive counterparts and is more commonly seen in alcohol withdrawal and substance intoxication [12].

Mixed delirium, as the name suggests, vacillates between hyper- and hypoactive subtypes of delirium and is the most commonly diagnosed subtype of delirium; presumably because the fluctuating change in mental status reminds practitioners of delirium [6]. Mixed delirium is also associated with deficits in orientation to time and place at admission, but there is no particular association with preexisting cognitive impairment [15]. Mixed delirium also seems to share more in common with hypoactive delirium with respect to outcomes. One study examining associations between delirium and mortality in terminally ill patients found a significant association between mixed delirium and shorter survival compared to hyperactive delirium [17].

Alternatively, emerging evidence suggests a fourth subtype of delirium exists called subsyndromal delirium and indicates the possibility there exists a spectrum of delirium ranging from normal to frank delirium [8]. In subsyndromal delirium, patients experience ≥1 symptom of delirium, such as deficits in cognition or attention, restlessness, anxiety, irritability, or hypersensitivity to stimuli, but they never reach diagnostic criteria as defined by the DSM-V [8, 18]. Although these patients fail to meet diagnostic criteria, they still experience worse outcomes compared to their unaffected counterparts [8]. As evidence accumulates, it is becoming apparent that delirium may not be as transient and reversible as previously thought [3]. Only 40% of patients experience complete resolution of symptoms by discharge. The remainder experience partial resolution of symptoms, which no longer qualify for a diagnosis of delirium, or no resolution of symptoms at 6- and 12-month follow-up [19–21].

Incidence, Prevalence, and Significance

Regardless of subtype, epidemiologic studies found delirium to be the most common complication of hospitalized elderly patients with 30–40% of cases being preventable [2, 21]. For hospital inpatients, the prevalence of delirium ranges from 11

to 42%; however, the prevalence of delirium *at* admission was 10–30% and was more common than the development of delirium *during* hospitalization [21, 22]. Other studies have found 7–9.6% of patients ≥65 have delirium on presentation to the ED, with the highest prevalence in frail elderly patients and those arriving from nursing homes; 60% and 40% respectively [2, 22]. Although these numbers are impressive, the prevalence of delirium in other acute care settings with sicker patients is even higher. More than 50% of elderly patients admitted to the ICU have delirium and delirium can be found in 80% of all ICU patients [8, 23]. Similarly, as high as 50% of postoperative elderly patients are diagnosed with delirium and the incidence of delirium varies depending on the procedure [24, 25].

Experiencing an incident of delirium itself is not without consequences. A single episode conveys an increased risk of mortality, institutionalization, permanent cognitive decline and dementia, with dementia patients experiencing the worst outcomes [2–4, 6, 20, 21, 26, 27]. Delirium lasting as short as 2–3 days confers these risks, with longer durations associated with poorer outcomes [2, 6, 20]. However, despite this association, other studies have shown the risk of death and institutionalization is independent of the duration of delirium, signifying that delirium as short as 1 day confers an increased risk for these outcomes [27].

ICU patients who develop delirium have a 2–4 times increased risk of mortality compared to their non-delirious counterparts. Similarly, hospital inpatients experience a 1.5 times increased risk [2]. The highest mortality risk is reserved for patients who arrive to the hospital or leave the hospital with delirium. Patients presenting to the ED with preexisting delirium experience a 70% increased risk of mortality at 6 months [2]. Similarly, patients who are discharged from the hospital to post-acute care settings in an unresolved delirious state experience both a fivefold increased risk in mortality at 6 months and an increased risk of institutionalization [2, 28]. Presumably, these findings can be explained by the fact that the sickest patients or elderly with poor cognitive reserve are more likely to succumb to delirium. However, studies have shown delirium is an independent risk factor for mortality and institutionalization, regardless of preexisting dementia, nursing home residence, age, sex, ethnicity, comorbid illnesses, or illness severity [27]. The most widely accepted explanation for this is that frail elderly patients, with poor cognitive reserve, need only minor insults to push them into delirium while young healthy patients, with robust cognitive reserve, need major insults to precipitate delirium. The magnitude of these insults may be associated with poorer long-term outcomes [2] (Fig. 7.1).

Many studies have shown delirium to be an independent risk factor for the development of dementia. It is also associated with an accelerated rate of cognitive decline over the ensuing 5 years with significantly worse global cognition and executive functioning [2–4, 6, 20, 21, 26, 27]. Accumulating evidence from a range of studies, including epidemiologic, neuropathological, and preclinical animal studies, suggests delirium results in permanent cognitive damage that differs from traditional dementia pathologies [2, 3, 26].

Davis et al. [26] performed a neuropathological, retrospective population based study of more than 500 patients to investigate the link between delirium and dementia. Interestingly, neuropathological correlates of dementia (e.g., neurofibrillary tau, amyloid burden, $APOE_4$ variants, vascular lesions, α-synuclein, and substantia nigra loss)

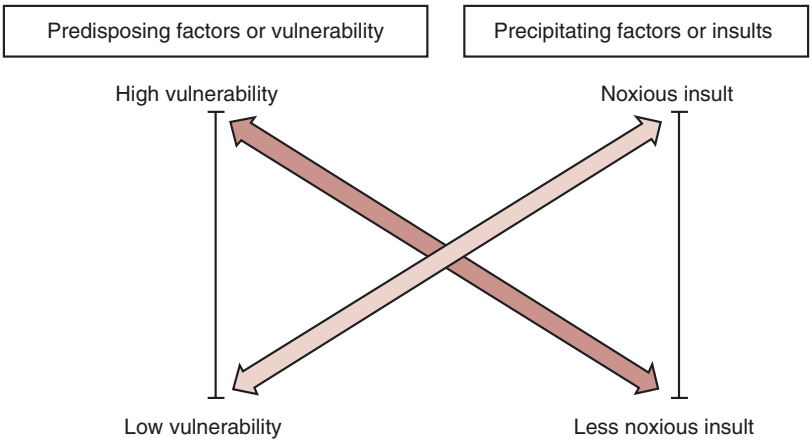

Fig. 7.1 Multifactorial model of delirium in older people. Onset of delirium is dependent on a complex interaction between the patient's baseline vulnerability (predisposing factors) at admission and precipitating factors or noxious insults occurring during hospital admission. Adapted from Inouye and Charpentier [29] by permission of the Journal of the American Medical Association

were strongest in dementia patients who had never experienced an episode of delirium. Dementia patients who had previously experienced delirium showed no significant association with these pathologies. It's important to note that the study was underpowered to detect an association, if it did exist; however, this brings up the possibility that dementia arising from delirium may result from alternative mechanisms of neuronal damage than traditional dementias [26]. Given the association between delirium and dementia and evidence suggesting delirium may result in organic insult to the brain, it prompts a new question. Are subsyndromal forms of delirium actually new cognitive baselines more consistent with new onset dementia than lingering delirium [3]?

In addition to patient morbidity from delirium, the healthcare system as a whole suffers the increased costs directly attributable to delirium [2, 12, 21, 30–32]. Not only does delirium complicate patient care by increasing the number of tests ordered in an attempt to determine the underlying etiology, but also predisposes patients to iatrogenic complications arising from those investigations ([6] intro story). As a result, delirious patients on average experience an 8-day increased length of stay [21]. The estimated monetary costs directly attributable to delirium was $164 billion annually in 2011 and the projected savings from decreasing incident delirium is estimated to be $16 billion per year in a 2015 study [2, 30, 31].

Risk Factors

Because the brain is a complex organ, understanding the complex interplay between various risk factors for acute brain failure is equally vexing. In general, risk factors for delirium can be categorized into predisposing and precipitating factors (Table 7.2).

Table 7.2 Summary of risk factors for delirium

Predisposing factors	Precipitating factors	Delirium-inducing medications
Comorbidities	Acute insults	High risk
Alcoholism	Dehydration	Anticholinergics (e.g., antihistamines, muscle relaxants, antipsychotics)
Chronic pain	Fracture	Benzodiazepines
History of baseline lung, liver, kidney, heart, or brain disease	Hypoxia	Dopamine agonists
Terminal illness	Infection	Meperidine (Demerol)
Demographic factors	Ischemia (e.g., cerebral, cardiac)	Moderate to low risk
Age older than 65 years	Medications	Antibiotics (e.g., quinolones, antimalarials, isoniazid, linezolid [Zyvox], macrolides)
Male sex	Metabolic derangement	Anticonvulsants
Geriatric syndromes	Poor nutrition	Antidizziness agents
Dementia	Severe illness	Antiemetics
Depression	Shock	Antihypertensives (e.g., beta blockers, clonidine [Catapres])
Elder abuse	Surgery	Antivirals (e.g., acyclovir [Zovirax], interferon)
Falls	Uncontrolled pain	Corticosteroids
History of delirium	Urinary or stool retention	Low-potency antihistamines (e.g., histamine H_2 blockers, urinary and gastrointestinal antispasmodics)
Malnutrition	Environmental exposures	Metoclopramide (Reglan)
Polypharmacy	Intensive care unit setting	Narcotics other than meperidine
Pressure ulcers	Sleep deprivation	Nonsteroidal anti-inflammatory drugs
Sensory impairment	Tethers	Sedatives/hypnotics
Premorbid state		Tricyclic antidepressants
Inactivity		
Poor functional status		
Social isolation		

Information from Refs. [4, 5, 25, 33]

Predisposing risk factors are preexisting, non-modifiable conditions that contribute to poor cognitive reserve and predispose a patient to delirium. Precipitating factors are modifiable insults experienced by an individual which provoke delirium and occur in all patient settings [22]. Previous studies have suggested that no single risk factor results in delirium, but rather a combination of risk factors may interact to incite delirium [22]. Predictive models have been generated and validated in predicting delirium in elderly medical inpatients and can be used to risk stratify patients into high, intermediate, and low risk categories on admission [6, 22, 34] (Table 7.3).

Table 7.3 Predictive model for the risk of delirium in hospitalized older patients

Risk factor	Points
Cognitive impairment (inability to think, concentrate, reason, remember, formulate ideas)	1
Elevated blood urea nitrogen/serum creatinine ratio (greater than 18)	1
Severe illness (APACHE score greater than 16, or nurse rating of severe)	1
Vision impairment (corrected near vision worse than 20/70 in both eyes)	1

Interpretation: 0 points = low risk (10% chance of developing delirium); 1 or 2 points = intermediate risk (25% chance of developing delirium); 3 or 4 points = high risk (80% chance of developing delirium)
APACHE acute physiology and chronic health evaluation (http://clincalc.com/IcuMortality/APACHEII.aspx)
Information from Ref. [1]

Management

Because the pathophysiology of delirium or the complex multifactorial interplay between risk factors is not fully understood, it seems intuitive that an effective approach to delirium must be equally broad and multifaceted [2, 35]. This requires multicomponent non-pharmacological interventions targeting various risk factors, as well as pharmacological interventions aimed at correcting the various neurotransmitter derangements implicated in the complex pathophysiology of delirium [22].

The current approach to managing delirium involves screening individuals using validated prediction models, early recognition of patients with delirium, and initiation of symptomatic and supportive measures while investigating for potential underlying causes [2, 6, 9]. The first task is determining who should be assessed for delirium at presentation and regularly throughout their hospital stay. Two models exist for risk stratifying patients and have overlapping features.

The first model, developed by Inouye et al. [34] and modified by Kalish et al. [6] in Table 7.3 has been previously validated. The second model is a part of the UK National Institute for Health and Clinical Excellence (NICE) 2010 guidelines for delirium and is based on 4 risk factors: (1) age 65 or older, (2) past or present cognitive impairment and/or dementia (must confirm with standardized measures), (3) current hip fracture, and (4) severe illness defined as any condition that is currently deteriorating or has the potential to deteriorate. According to the NICE [9] guidelines, the presence of any one of these four risk factors places the patient at high risk and should be regularly assessed for delirium throughout their stay.

Once patients have been risk stratified, patients who are deemed high risk should be assessed for delirium within 24 h of admission and throughout their hospital stay using the patient's history from an informed observer (e.g., family, caregiver, staff) and a bedside cognitive assessment (e.g., CAM) [2, 6, 9]. CAM is the most effective tool for identifying delirium, both at presentation and throughout hospital admission, and has a sensitivity of 94% and specificity of 89% [6, 16]. However, a high index of clinical suspicion must be maintained for these patients because solely relying on CAM may miss hypoactive cases of delirium. As stated previously, hypoactive delirium is more common in elderly persons and associated with the poorest outcomes [2, 5, 6]. If the patient undergoing assessment is lethargic

(i.e., can't complete an interview), it should be assumed they are delirious until proven otherwise [2].

Performing initial assessments is crucial to the management of delirium because it establishes the patient's baseline mental status and allows recognition of fluctuations in cognition and other features of delirium that may arise during hospitalization [2, 6]. Moreover, many features of delirium overlap with dementia and bedside cognitive assessments cannot distinguish between the two since they only differ in acuity of mental status change. Only an accurate history can differentiate delirium from dementia and this is critical since preexisting cognitive impairment or dementia is the strongest risk factor for developing delirium [3, 22, 32].

Once the diagnosis of delirium has been made, the next step is to determine the underlying cause and begin appropriate investigations [2, 6, 9] (Table 7.4; Fig. 7.1). The patient's chief complaint, medical history, and physical exam should guide clinical investigations because an unguided workup will likely result in low yields [2]. Basic workup includes vitals, blood sugar, electrolytes, complete blood count, hepatic and renal panels, urinalysis, and electrocardiogram, with any additional diagnostic tests individualized to the patient [2, 6].

EEG has poor sensitivity and specificity for diagnosing delirium; however, diffuse slowing with increased theta and delta activity is characteristic of delirium. EEG background rhythm organization correlates with delirium severity. EEG is not useful for distinguishing between subtypes of delirium, but it may help diagnose non-convulsive status epilepticus (NCSE) or differentiate between psychogenic and organic causes of altered mental status [2].

Brain imaging with non-contrast CT or MRI is generally not indicated and low yield in non-select patients. Results are unrevealing in 98% of patients with preexisting dementia in the absence of focal deficits and in delirious patients with a previously identified cause for their delirium [2, 36, 37]. The strongest indication to order neuroimaging in patients with altered mental status is the presence of focal neurological deficits because stroke and intracranial hemorrhage may present as delirium [2, 36, 37]. Other indications include patients with a recent history of fall or signs of fall, recent head trauma, fever with suspicion for encephalitis, or depressed consciousness without an identifiable cause. Lumbar puncture should be reserved for patients with suspected CNS infections or subarachnoid hemorrhage, and may be useful in cases of persistent delirium when no cause can be identified [2].

Treatment

During the search for an etiology, initiation of first line treatment with supportive care, multicomponent non-pharmacologic interventions, and complication prevention should be initiated [6] (Table 7.4). The purpose of multicomponent interventions is to focus on changing the modifiable risk factors of the patient and care should be individualized to each patient [9]. Current recommendations advocate for multicomponent interventions to be implemented by a trained interdisciplinary team [2, 5, 6, 9]. Patient medications should be reviewed and the only pharmacological aspect of multicomponent interventions is adequate pain control, which may

Table 7.4 Interventions to prevent and treat delirium

Cognitive impairments or disorientation	*Infection*
Provide consistency in health care by limiting the number of staff and minimizing turnover	Assess for and treat infection
Provide appropriate lighting and clear signage	Avoid unnecessary catheterization
Provide a working/accurate clock and up-to-date calendar in patient's room	Implement infection control
Orient and reorient patients by explaining where they are, who they are, and the clinician's role in their health care	*Pain*
Introduce cognitively stimulating activities	Continually assess for verbal and nonverbal signs of pain
Encourage/facilitate regular visits from family and friends	Initiate and reevaluate for appropriate pain management
Provide one-on-one care, if needed	Avoid as-needed orders and consider using stop/hold orders
Dehydration/constipation	*Poor nutrition*
Encourage patient to drink adequate fluids	Provide adequate supplementation between meals, and culturally sensitive meal choices
Consider subcutaneous or intravenous fluids (to ensure adequate fluid intake and prevent dehydration) if the patient is unable to adequately hydrate by mouth	Encourage presence of family members at meal times
Consult specialists if patient has comorbidities that would affect fluid balance (e.g., congestive heart failure, chronic kidney disease)	Ensure patient has dentures that fit properly (if needed)
Hypoxia	*Sensory impairment*
Assess for hypoxia	Ensure hearing and visual aids are available and in proper working condition
Optimize oxygen saturation as appropriate	*Sleep*
Immobility or limited mobility	Promote good sleep patterns
Encourage early mobilization and active range-of-motion exercises	Avoid nursing or medical procedures during sleeping hours
	Schedule medication rounds to avoid sleep disturbances
	Reduce noise to a minimum during sleep periods
	Ensure proper and predictable sleep–wake cycles and avoid the patient napping

Information from Refs. [28, 32, 33, 36]

include the use of narcotics. Although narcotics may precipitate delirium, uncontrolled pain may also provoke delirium so the decision is ultimately based on clinical judgement [6, 9]. Despite the accepted practice standard to initiate multicomponent interventions, evidence to date remains inconclusive these interventions are effective

in treating delirium; however, they may be initiated regardless because these interventions are analogous to good basic medical care [22, 35, 38].

Currently, there is no convincing evidence that pharmacological interventions intended to treat symptoms of delirium are effective or have any impact on mortality, ICU admission rate, complications, or length of stay [2, 9, 22, 35]. The symptoms of hyperactive delirium often attract the attention of medical personnel, leading to the prescription of antipsychotics and benzodiazepines to control these bothersome symptoms [39]. However, it is likely this only serves to transform their hyperactive delirium into hypoactive delirium (which is then not measured), thereby effectively treating their symptoms [2, 35]. This likely explains why the general consensus and expert opinion is to use antipsychotic medications to control symptoms of delirium [2, 40].

The first line treatment for agitated patients is nonpharmacological behavioral interventions [2, 5, 9]. This includes interventions in (Tables 7.4 and 7.5; Fig. 7.2) and using verbal and non-verbal techniques to de-escalate the situation [9, 41]. It is important to address any underlying triggers for aggression, such as excessive nighttime blood draws or uncontrolled pain, and best practice guidelines recommend avoiding the use of physical restraints at all costs [2, 3, 6, 9]. Physical restraints may worsen agitation and are not only a risk factor for delirium in itself, but also impair mobility and increase the risk for pressure ulcers among other complications [2, 3, 5, 6, 9, 22, 34, 42].

If these interventions have failed, then pharmacological options be considered and restricted to patients who pose a *substantial threat* to themselves or others [2, 5, 9]. Hallucinations and delusions themselves are not indications for antipsychotics and should only be used if they become extremely distressing to the patient or interfere with care [2]. Guidelines recommend starting at the lowest dose and slowly titrating to the lowest effective dose, with treatment lasting less than 1 week if pos-

Table 7.5 DSM-5 diagnostic criteria for delirium

A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)
D. The disturbances in criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies

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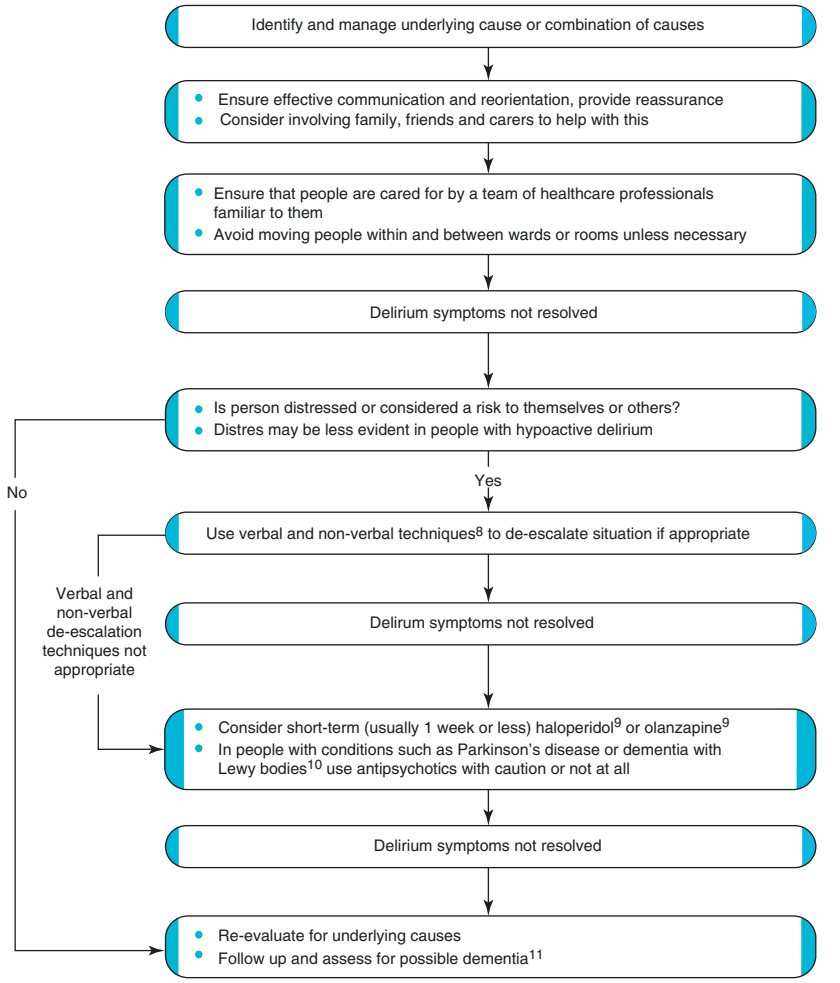

[8]See 'Violence' (NICE clinical guidelines 25).
[9]Haloperidol and olanzapine do not have UK marketing authorisation for this indication.
[10]For more information on the use of antipsychotics for these conditions, see 'Parkinson's disease' (NICE clinical guideline 35) and 'Dementia' (NICE clinical guideline 42).
[11]For more information on dementia see 'Dementia' (NICE clinical guideline 42).

Fig. 7.2 Treating delirium

sible. Once medication has been initiated, daily assessments must be made to determine the soonest possible time to discontinue therapy [5, 9]. Conventionally, haloperidol has been the drug of choice for this indication but there is no good data to guide selection of an antipsychotic agent [6]. Studies have shown haloperidol, quetiapine, and ziprasidone did not have higher rates of delirium resolution compared to placebo and recent data for olanzapine suggests it may actually increase

the duration and severity of delirium [2, 33, 39, 43, 44]. Alternatively, other medications such as benzodiazepines may be considered for agitated patients, but the American Geriatric Society does not recommend using benzodiazepines as first line treatment for agitated patients unless there are other indications (e.g., alcohol withdrawal) [5].

Prevention

Given the adverse outcomes, increased costs, and ineffective treatment for delirium once it develops, much of the recent literature has shifted to focus on prevention rather than treatment [22]. An overwhelming amount of data supports the utility and efficacy of multicomponent interventions targeted towards modifying evidence based risk factors and the widest used model is the Hospital Elder Life Program (HELP) ([2, 5, 9, 22, 30, 38, 42]).

The HELP program focuses on six risk factors for delirium (see Table 7.6) and was originally designed to address the full spectrum of geriatric issues and iatrogenic problems that contribute to cognitive and functional decline during hospitalization of the elderly (Inouye 2000). HELP interventions are implemented by a trained interdisciplinary team, which includes specially trained geriatric Elder Life Specialist nurses and trained volunteers. They are designed to integrate into existing hospital frameworks without the addition of a geriatric consultation service (Inouye 2000). More than 200 hospitals have adopted the program worldwide and each institution is encouraged to make individual adaptations respective to their unique healthcare settings [2].

The HELP program, which consists of multicomponent non-pharmacologic interventions, is the only intervention which has repeatedly proven effective in preventing delirium across medical and surgical wards and is not affected by preexisting dementia [22, 42]. HELP also decreases the odds of falling and studies estimate HELP interventions prevent 4.26 falls per 1000 patient days, saving $9000 per patient year [2, 30].

Despite the promise of multicomponent interventions in the prevention of delirium, the evidence to date does not support the effectiveness of these interventions for the treatment of delirium [38]. Multiple studies have shown multicomponent interventions have no impact on hospital length of stay, likelihood of return to independent living, duration of delirium, institutionalization or mortality (either inpatient or at 12-months) [22, 38, 42]. However, a recent Cochrane review found the evidence for some of these findings remains inconclusive as a result of significant heterogeneity across studies due to the un-blinded nature of the intervention, unequal prevalence of dementia between groups, and imprecise results, calling for a need for more research [22]. Similarly, there is not enough evidence to assess the relative contribution of each individual intervention to the overall effectiveness of multicomponent interventional therapy [38].

Table 7.6 Risk factors and interventions

Risk factor	Type of intervention
Cognitive impairment	Use reality orientation and cognitive stimulating activities [40]
Vision/hearing impairment	Ensure patient has his/her eyeglasses, hearing aids
Immobilization	Get patient moving
	Avoid restraints
Dehydration	Identify dehydration early and replace lost fluids
Psychoactive medication use	Use nonpharmacologic methods to treat anxiety and sleeplessness
Sleep deprivation	Employ noise reduction strategies, and prevent day and night reversal with good sleep hygiene

Source: http://www.the-hospitalist.org/wp-content/uploads/2015/10/TH_1015_pg22e.png

In addition to multicomponent interventions, studies have also assessed ways to decrease incidence of perioperative delirium by employing bispectral index (BIS) monitoring during anesthesia and lighter sedation with surgery [45–47]. There is moderate quality evidence that BIS-guided anesthesia not only decreases incident cases of delirium, but also decreases hospital length of stay and improves cognitive outcomes at 7 days and 3 months [5, 22]. Consistent with this, the American Geriatric Society has adopted BIS-guided anesthesia for elderly patients as a part of their recommended guidelines for preventing postoperative delirium. Light propofol sedation during surgery has shown similar results. However, there are serious concerns regarding inadequate sedation such as intraoperative recall by patients, patient movement during a critical point of the surgery, and excessive sympathetic stimulation leading to tachycardia and hypertension. As a result, the American Geriatric Society has refrained from making any practice recommendations [5, 22].

Pharmacologic prevention strategies have also been studied to assess their efficacy in preventing delirium but the overall body of evidence remains limited secondary to poor study design, heterogeneity, failure to screen for delirium at baseline, and exclusion of dementia patients from studies [22]. Due to the similar characteristics between dementia and delirium, many studies exclude patients with preexisting dementia to facilitate accurate diagnoses of delirium. However, this may skew results since the prevalence of delirium is higher in this population and associated with poorer outcomes. This conceivably limits the generalizability of these studies, since the study samples are not representative of the actual population of elderly adults who experience delirium [22, 35]. Moreover, a significant portion of studies failed to screen for delirium at baseline. Given that almost 10% of elderly patients present to the hospital with preexisting delirium, failure to screen for delirium at intake may have prevented statistical significance in these studies (an intervention cannot have an impact on preventing delirium if the outcome was already present but not measured) [22]. As a result, more evidence is needed before guidelines can be recommended to influence practice [5, 9, 22]. In spite of this, an overview of various drug interventions has been included for completeness.

Prevention studies for typical and atypical antipsychotics are inconclusive and study outcomes are inconsistent with conflicting results [22]. There is no clear evidence that antipsychotics, as a class of medications, are effective in preventing delirium [5, 9, 22]. Moderate quality evidence exists for olanzapine decreasing incident cases of delirium. However, it may also worsen the severity and duration of delirium and requires more evidence before recommendations are made [22].

Donepezil has inconsistent results for preventing delirium, but some of these studies have been underpowered. Additionally, very low quality evidence suggests donepezil may decrease the severity of delirium and length of stay [22, 29]. Alternatively, studies with rivastigmine have shown it may increase mortality and duration of delirium [2].

Studies examining the effects of melatonin (i.e., ramelteon) have very low quality evidence demonstrating no clear benefit for prevention or limiting severity of delirium, and stronger evidence suggests it has no effect on duration of delirium or length of stay [22]. One study evaluating citicoline, which is believed to stabilize cell membranes and scavenge free radicals, found no evidence it was effective in preventing delirium [22, 48]. Other studies examining methylprednisolone in high risk patients undergoing cardiopulmonary bypass found no effect on the incidence of delirium, length of stay, or 30-day mortality [22, 49].

Lastly, multiple studies have assessed opioid sparing measures as a means to prevent postoperative delirium but the evidence remains inconclusive [22]. Studies examining gabapentinoids (i.e., gabapentin and pregabalin) as adjunctive therapy were limited to single studies or small sample sizes, and the host of studies which have examined pregabalin for postoperative pain did not assess for delirium specifically [22, 50, 51]. A small study examined the use of adjunctive ketamine for postoperative pain management and found ketamine was associated with an increased incidence of delirium. However, the evidence is inconclusive and deemed very low quality evidence by a Cochrane review [22, 52].

Another limited study assessed the effects of intrathecal morphine compared to PCA but failed to show any clear evidence of benefit [22, 53]. A small study assessed parecoxib adjunctive treatment compared to morphine and placebo (i.e., no more pain treatment) and showed a decreased incidence of delirium in the parecoxib group but the methodological limitations hinder the usefulness of these findings [22, 54]. Conversely, a study with moderate quality evidence examined the utility of regional anesthetic pain control versus an opioid based regimen for pain in patients with hip fractures and found fascia ilia compartment block (FICB) decreased the incidence of delirium [7, 22]. Consistent with the heterogeneous findings of these studies, the American Geriatric Society recommends optimization of postoperative pain with preferably non-opioid regimens for elderly patients, but does not specify which medications to use other than regional anesthetic blocks by healthcare professionals trained in the procedure [5].

Conclusion

Traditionally, prevention and treatment of delirium has been based on expert opinion rather than empirical data. But as evidence accumulates, the approach to delirium is shifting to prevention rather than treatment, as an effective "cure" for delirium does not exist [35]. The only strong evidence for preventing delirium to date are multicomponent interventions, the most popular of which is the HELP program [22].

Central to the HELP program is a holistic, patient-centered approach, which strives to create a therapeutic environment for the patient. Some argue HELP interventions have merely operationalized elements of good basic medical care that all patients should be receiving in the first place [35]. Although these interventions have yet to be proven effective in the treatment of delirium, consensus still favors a multifaceted approach to address the complex multifactorial etiologies of delirium [2, 35].

The overall body of evidence does not support the use of antipsychotics for the prevention of delirium in non-ICU hospitalized patients but the poor quality of evidence limits the ability to make practice recommendations [22]. Similarly, the general consensus for antipsychotics in the treatment of delirium should be used as a last resort, reserved for patients who pose a significant threat to themselves or others and have no efficacy decreasing the incidence, severity, or duration of delirium [5, 22]. Rather than the dogmatic pharmacological approach to delirium, overall focus should be on prevention, with management of delirium centered on enhancing patient recovery, maximizing functional status, and improving clinical outcomes for geriatric patients [2].

Key Points

- Assessment for delirium should occur at intake and repeatedly throughout admission of high risk patients as identified by validated screening tools.
- Detection and management of delirium requires the entire health team. Physicians who see the patient briefly throughout the day may miss the acute, fluctuating symptoms of delirium. Nurses should be trained to recognize delirium and initiate nonpharmacological interventions.
- The Confusion Assessment Method (CAM) is the most widely used bedside assessment tool for delirium, but strict reliance on a single test alone may miss some cases of hypoactive delirium. Collateral history from family and daily assessment of orientation to time and place may improve detection rates for hypoactive delirium.
- Multicomponent interventions are the only effective means of preventing delirium and should be adopted by hospitals and implemented by an interdisciplinary

team. The Hospital Elder Life Program (HELP) is the most well studied and can be tailored to specific hospitals.

- No evidence supports the use of antipsychotics to prevent delirium and should be reserved as a last resort for patients who pose a significant risk to themselves in the treatment of delirium.

References

1. American Psychiatric Association. Diagnostic and statistical manual. 5th ed. Washington, DC: APA Press; 2013.
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911–22.
3. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. Lancet Neurol. 2015;14(8):823–32.
4. Gross AL, Jones RN, Habtemariam DA, Fong TG, Tommet D, Quach L, Schmitt E, Yap L, Inouye SK. Delirium and long-term cognitive trajectory among persons with dementia. Arch Intern Med. 2012;172(17):1324–31.
5. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. J Am Coll Surg. 2015;220(2):136–48.e1.
6. Kalish VB, Gillham JE, Unwin BK. Delirium in older persons: evaluation and management. Am Fam Physician. 2014;90(3):150–8.
7. Mouzopoulos G, Vasiliadis G, Lasanianos N, Nikolaras G, Morakis E, Kaminaris M. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. J Orthop Traumatol. 2009;10(3):127–33.
8. Morandi A, Jackson JC. Delirium in the intensive care unit: a review. Neurol Clin. 2011;29(4):749–63.
9. National Institute for Health and Clinical Excellence. Delirium: diagnosis, prevention and management CG103. London: National Institute for Health and Clinical Excellence; 2010.
10. Farrell KR, Ganzini L. Misdiagnosing delirium as depression in medically ill elderly patients. Arch Intern Med. 1995;155(22):2459–64.
11. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med. 1994;97:278–88.
12. Peritogiannis V, Bolosi M, Lixouriotis C, Rizos DV. Recent insights on prevalence and corelations of hypoactive delirium. Behav Neurol. 2015;2015:416792.
13. Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. Palliat Med. 2006;20(1):17–23.
14. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med. 2009;35(7):1276–80.
15. Gabriel FJ, Santesteban O, Trzepacz P, Bernal C, Valencia C, Ocampo MV, Pablo JD, Gaviria AM, Vilella E. MMSE items that predict incident delirium and hypoactive subtype in older medical inpatients. Psychiatry Res. 2014;220(3):975–81.
16. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The confusion assessment method: a systematic review of current usage. J Am Geriatr Soc. 2008;56(5):823–30.
17. Kim SY, Kim SW, Kim JM, Shin IS, Bae KY, Shim HJ, Bae WK, Cho SH, Chung IJ, Yoon JS. Differential associations between delirium and mortality according to delirium subtype and age: a prospective cohort study. Psychosom Med. 2015;77(8):903–10.
18. DeCrane SK, Culp KR, Wakefield B. Twelve-month mortality among delirium subtypes. Clin Nurs Res. 2011;20(4):404–21.

19. Cole M, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age Ageing. 2009;38(1):19–26.
20. McCusker J, Cole M, Dendukuri N, Han L, Belzile E. The course of delirium in older medical inpatients. J Gen Intern Med. 2003;18(9):696–704.
21. Siddiqi N, House AO, Holmes J. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350–64.
22. Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA. Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev. 2016;3:CD005563.
23. Morandi A, Jackson JC, Ely EW. Delirium in the intensive care unit. Int Rev Psychiatry. 2009;21(1):43–58.
24. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. J Am Geriatr Soc. 2006;54(10):1578–89.
25. Fok MC, Sepehry AA, Frisch L, Sztramko R, Borger van der Burg BL, Vochteloo AJ, Chan P. Do antipsychotics prevent postoperative delirium? A systematic review and meta-analysis. Int J Geriatr Psychiatry. 2015;30(4):333–44.
26. Davis DH, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, Cunningham C, Polvikoski T, Sulkava R, MacLullich AM, Brayne C. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. Brain. 2012;135(Pt 9):2809–16.
27. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304(4):443–51.
28. McAvay GJ, Van Ness PH, Bogardus ST Jr, Zhang Y, Leslie DL, Leo-Summers LS, Inouye SK. Older adults discharged from the hospital with delirium: 1-year outcomes. J Am Geriatr Soc. 2006;54(8):1245–50.
29. Liptzin B, Laki A, Garb JL, Fingeroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry. 2005;13(12):1100–6.
30. Hshieh TT, Yue J, Oh E, Puelle M, Dowal S, Travison T, Inouye SK. Effectiveness of multicomponent nonpharmacological delirium interventions. JAMA Intern Med. 2015;175(4):512–20.
31. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008;168(1):27–32.
32. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013;21(12):1190–222.
33. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW, MIND Trial Investigators. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010;38(2):428–37.
34. Inouye SK, Zhang Y, Jones RN, Kiely DK, Yang F, Marcantonio ER. Risk factors for delirium at discharge: development and validation of a predictive model. Arch Intern Med. 2007;167(13):1406–13.
35. Quinn TJ. Forward thinking: where next for delirium prevention research? Cochrane Database Syst Rev. 2016;3:ED000110.
36. Hirano LA, Bogardus ST Jr, Saluja S, Leo-Summers L, Inouye SK. Clinical yield of computed tomography brain scans in older general medical patients. J Am Geriatr Soc. 2006;54(4):587–92.
37. Hufschmidt A, Shabarin V. Diagnostic yield of cerebral imaging in patients with acute confusion. Acta Neurol Scand. 2008;118(4):245–50.
38. Abraha I, Trotta F, Rimland JM, Cruz-Jentoft A, Lozano-Montoya I, Soiza RL, Pierini V, Dessì Fulgheri P, Lattanzio F, O'Mahony D, Cherubini A. Efficacy of non-pharmacological interventions to prevent and treat delirium in older patients: a systematic overview. The SENATOR project ONTOP Series. PLoS One. 2015;10(6):e0123090.
39. Friedman JI, Soleimani L, McGonigle DP, Egol C, Silverstein JH. Pharmacological treatments of non-substance-withdrawal delirium: a systematic review of prospective trials. Am J Psychiatry. 2014;171(2):151–9.

40. Bush SH, Kanji S, Pereira JL, Davis DH, Currow DC, Meagher DJ, Rabheru K, Wright DK, Bruera E, Agar M, Hartwick M, Gagnon PR, Gagnon B, Breitbart W, Regnier L, Lawlor PG. Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. J Pain Symptom Manag. 2014;48(2):231–48.
41. National Institute for Health and Clinical Excellence. Short-term management in mental health, health and community settings NG10. London: National Institute for Health and Clinical Excellence; 2015.
42. Martinez F, Tobar C, Hill N. Preventing delirium: should non-pharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature. Age Ageing. 2015;44(2):196–204.
43. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2010;38(2):419–27.
44. Tahir TA, Eeles E, Karapareddy V, Muthuvelu P, Chapple S, Phillips B, Adyemo T, Farewell D, Bisson JI. A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. J Psychosom Res. 2010;69(5):485–90.
45. Chan MT, Cheng BC, Lee TM, Gin T, CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013;25(1):33–42.
46. Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth. 2013;110(S1):i98–i105.
47. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, Mears SC. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc. 2010;85(1):18–26.
48. Fioravanti M, Buckley AE. Citicoline (Cognizin) in the treatment of cognitive impairment. Clin Interv Aging. 2006;1(3):247–51.
49. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum Á, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S. Yusuf S; SIRS investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386(10000):1243–53.
50. Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB, Ames C, Chou D, Weinstein P. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology. 2006;67(7):1251–3.
51. Pesonen A, Suojaranta-Ylinen R, Hammarén E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. Br J Anaesth. 2011;106(6):873–81.
52. Urban MK, Ya Deau JT, Wukovits B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. HSS J. 2008;4(1):62–5.
53. Beaussier M, Weickmans H, Parc Y, Delpierre E, Camus Y, Funck-Brentano C, Schiffer E, Delva E, Lienhart A. Postoperative analgesia and recovery course after major colorectal surgery in elderly patients: a randomized comparison between intrathecal morphine and intravenous PCA morphine. Reg Anesth Pain Med. 2006;31(6):531–8.
54. Li J-Z, Li X-Z, Wang X-M, Wang M-S, Yu H-F, Shi F, et al. Effects of parecoxib sodium analgesia on serum concentrations of neuron-specific enolase and S-100^{b} and postoperative cognitive function of elderly patients undergoing acute replacement of femoral head. [Chinese]. Zhonghua Yi Xue Za Zhi. 2013;93(27):2152–4.

Chapter 8
Update in the Treatment of Sepsis and Septic Shock: Transitioning from SIRS to SOFA

Gyorgy Frendl and Daniela Lazea

Introduction

There are several outcome prediction models that are currently available for use in clinical practice. The widely used SIRS was introduced to a larger audience in 1991 at the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference with the goal of aiding in the early detection of sepsis. The use of the SIRS criteria is highly sensitive, as >90% of patients admitted to the ICU meet the SIRS criteria. The use of SIRS has been especially beneficial in the early diagnosis of sepsis.

The Sequential Organ Failure Assessment (SOFA) score is an objective score that allows for calculation of both the number and the severity of organ dysfunction. It has been promoted as a more specific marker of sepsis and has been validated by large retrospective studies. The qSOFA, quick sequential organ assessment, score is easier to calculate bedside assessment that may identify patients with suspected infection who are at greater risk for a poor outcome outside the intensive care unit (ICU). The following chapter explains the SOFA and qSOFA score to identify sepsis and the current recommendations and supporting evidence in the treatment of sepsis.

Sepsis and Septic Shock: Defining the Conditions

- *Sepsis*: is a condition of life-threatening organ dysfunction (such as hypotension, altered mentation, oliguria, and others) due to a dysregulated host response to infection (confirmed or suspected). This is defined by the quick sequential sepsis

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related organ failure assessment (qSOFA) score. Organ dysfunction can be broadly defined as an acute change of ≥2 points of the SOFA score (see components of SOFA score and the scoring tables below). An increase of ≥2 points in the SOFA score is associated with a 10% expected mortality (JAMA 2016; 315(8):801–810). SOFA score is assumed to be 0 for patients who are known NOT to have organ dysfunction at the first encounter.

- *Septic Shock*: is a severe form of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to cause a substantial increase in mortality.
- Septic shock is characterized by refractory hypotension and vasopressor requirement (hemodynamic instability) despite sufficient iv fluid resuscitation (20 ml/kg of colloids or 40 ml/kg of crystalloids) to maintain a mean arterial pressure (MAP) ≥65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dl). Patients who meet these criteria have an expected mortality of 30–40% (variable by geography and level of organized sepsis care).

The new 2016 sepsis guidelines (Sepsis-3; JAMA 2016; 315(8):801–810) were intended to increase the precision and speed of sepsis diagnosis. They shifted the diagnostic focus to infection-triggered organ dysfunction (from systemic inflammation), and eliminated the categories of SIRS and severe sepsis, leaving sepsis and septic shock as the two entities of the sepsis spectrum.

Diagnostic Guide for Identifying Patients with Sepsis

For patients with a diagnosed or suspected infection the diagnosis of sepsis should be established by the presence of organ dysfunction as reflected by an increase from their baseline score of ≥2 points:

- In their qSOFA score if they are outside of the ICU (or in the absence of laboratory data enabling the use of the more detailed SOFA score)
- In their SOFA score if they are in the ICU or have data enabling the use of the more detailed SOFA score

See website for a calculator for SOFA and qSOFA: http://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score.

qSOFA (quick Sequential [sepsis-related] Organ Failure Assessment) score is calculated from (range 0–3 points; JAMA 2016; 315(8):801–810) the below physiologic signs, one point granted for each criteria met:

- Respiratory rate ≥22
- Systolic BP ≥100
- Any altered mental status (or Glasgow Coma Scale (GCS) ≤ 13 if established)

SOFA score ranges between 0–24 points (Intensive Care Med. 1996;22:707) and has the following components (see Table 8.1):

Recommended strategies for the early diagnosis of sepsis (Sepsis-3—JAMA 2016; 315(8):801–810). See Fig. 8.1.

Table 8.1 Components of sofa score

	0	1	2	3	4
Respiratory PaO_2/FiO_2	>400	<400	<300	<200	<100
Cardiovascular (doses in mcg/kg/min)	No hypotension	MAP < 70	Dopamine < 5 or dobutamine (any dose)	Dopamine > 5 or norepinephrine < 0.1	Dopamine > 15 or norepinephrine > 0.1
Coagulation PLT > 100,000	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dl)	<1.2	1.2–1.9	2–5.9	6–11.9	>12
CNS GCS	15	13–14	10–12	6–9	<6
Renal creatinine (mg/dl)	<1.2	1.2–1.9	2–3.4	3.5–4.9	>5

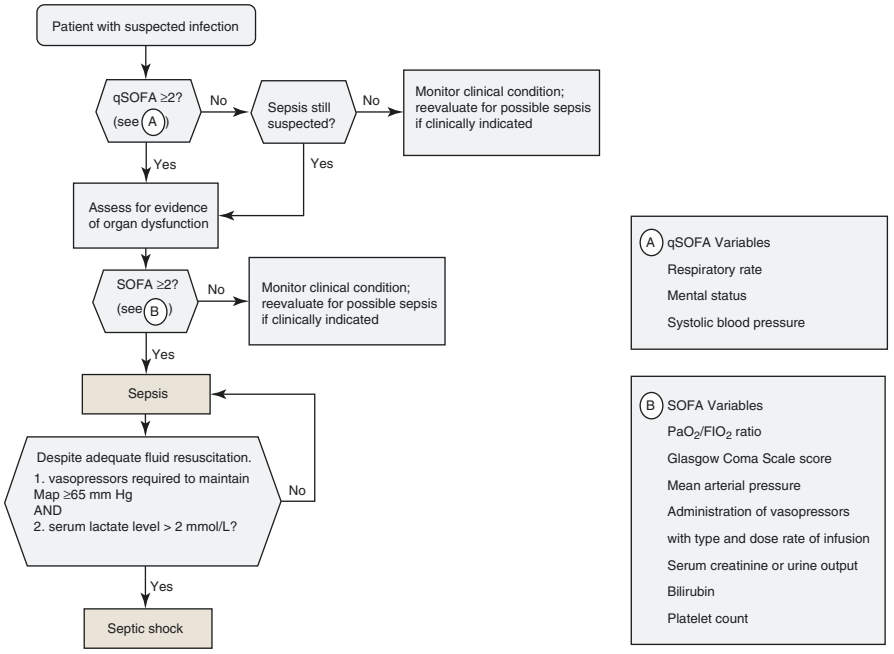

Fig. 8.1 Operationalization of clinical criteria identifying patients with sepsis and septic shock

Summary of Recommendations: Surviving Sepsis Campaign 2016

Initial Resuscitation

Sepsis and septic shock are medical emergencies, and treatment should begin immediately. While recent studies did not show benefits to a protocol-based fluid replacement strategy (NEJM 2014; 370(18):1683–1693) judicious, early fluid resuscitation has become the standard of care now and it has improved the outcomes of sepsis (as large observational studies have documented).

In the resuscitation from sepsis induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 h (strong recommendation, low quality of evidence). Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of hemodynamic status.

Early fluid resuscitation should begin immediately as shock is diagnosed for septic patients (persistent hypotension, or if blood lactate >4 mmol/L).

The goals of quantitative resuscitation during the first 6 h of management are (1C):

- Target mean arterial pressure of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).
- Normalization of lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).
- Central venous (sup. Vena cava) oxygen saturation ($ScvO_2$) ≥70% or mixed venous oxygen saturation (SvO_2) ≥65 mm Hg.

The use of CVP alone to guide fluid resuscitation can no longer be justified because the ability to predict a response to a fluid challenge when the CVP is within a relatively normal range (8–12 mm Hg) is limited (Cecconi M, De Backer D, Antonelli M, et al.: Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2014; 40:1795–1815).

Dynamic measures of assessing whether a patient requires additional fluid have been proposed in an effort to improve fluid management and have demonstrated better diagnostic accuracy at predicting those patients who are likely to respond to a fluid challenge by increasing stroke volume. These techniques encompass passive leg raises, fluid challenges against stroke volume measurements, or the variations in systolic pressure, pulse pressure, or stroke volume to changes in intrathoracic pressure induced by mechanical ventilation (Cecconi M, Hofer C, Teboul JL, et al.; FENICE Investigators; ESICM Trial Group: Fluid challenges in intensive care: the FENICE study: A global inception cohort study. *Intensive Care Med* 2015; 41: 1529–1537).

Diagnostic Workup

- Appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock, if doing so results in no substantial delay in the start of antimicrobials.

Appropriate routine microbiologic cultures always include at least two sets of peripheral blood cultures (aerobic and anaerobic). Additional diagnostic imaging studies can be obtained after the patient is stabilized and is safe to move.

Antibiotic Therapy

- Administration of IV antimicrobials should be initiated as soon as possible after recognition and preferably within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence).
- Empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock should cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).

The empiric antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.

- Combination therapy for the routine treatment of neutropenic sepsis/bacteremia should not be used (strong recommendation, moderate quality of evidence).
- Antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence). Longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia (weak recommendation, low quality of evidence).
- Measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence). Procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence)

Source Control

- Specific anatomical diagnosis of infection should be sought (e.g., necrotizing soft tissue infection, peritonitis with intra-abdominal infection, cholangitis, intestinal infarction, etc.) or ruled out, and emergent source control be sought as rapidly as possible (Crit Care Med. 2008;36:296)
- Removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established.

Fluid Therapy

- A fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve.
- Crystalloids are the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
- Balanced crystalloids or saline can be used for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
- Albumin can be used in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock, when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).
- We recommend against using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).

Vasopressor Therapy and Vasopressors

- Norepinephrine should be the first-line pressor used (strong recommendation, moderate quality of evidence).
- Vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) should be added to norepinephrine with the intent of raising mean arterial pressure to target.
- The use of dopamine (as an alternative to norepinephrine) is only suggested for highly selected pts. at very low risk of arrhythmias, with bradycardia (weak recommendation, low quality of evidence). Dopamine should not be used for renal protection.
- Dobutamine should be used in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).
- If initiated, dosing should be titrated to an end point reflecting perfusion, and the agent reduced or discontinued in the face of worsening hypotension or arrhythmias.

All patients requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available (weak recommendation, very low quality of evidence).

Blood Product Administration

- RBC transfusion should occur only when hemoglobin concentration decreases to <7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence).

- Erythropoietin should not be used for treatment of anemia associated with sepsis (strong recommendation, moderate quality of evidence).
- Fresh frozen plasma should not be used to correct clotting abnormalities in the absence of bleeding or planned invasive procedures (weak recommendation, very low quality of evidence).
- Prophylactic platelet transfusion should be administered when counts are <10,000/mm^3 (10 × 109/L) in the absence of apparent bleeding and when counts are <20,000/mm^3 (20 × 109/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥50,000/mm^3) are advised for active bleeding, surgery, or invasive procedures (weak recommendation, very low quality of evidence).

Mechanical Ventilation, Sepsis-Induced ARDS

- Use 6 ml/kg tidal volumes for pts. with ARDS or at risk of ARDS (some exceptions are acceptable based on pt. respiratory drive) (strong recommendation, high quality of evidence), and to maintain plateau pressures of <30 cm H_2O (in pts. with normal extrapulmonary compliance) (strong recommendation, moderate quality of evidence)
- Higher levels of positive end-expiratory pressure (PEEP) should be used when higher FiO_2 is required for pts. with more severe ARDS (weak recommendation, moderate quality of evidence).
- High-frequency oscillatory ventilation should not be used in adult patients with sepsis-induced ARDS (strong recommendation, moderate quality of evidence).
- May use recruitment maneuvers for pts. with severe refractory hypoxemia (weak recommendation, moderate quality of evidence).
- Suggest prone positioning for pts. with very severe ARDS PaO_2/FiO_2 < 150 after recruitment maneuvers in facilities with experience with such practices (weak recommendation, moderate quality of evidence).
- Mechanically ventilated sepsis patients should be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (strong recommendation, low quality of evidence).
- Neuromuscular blocking agents can be used for ≤48 h in adult patients with sepsis-induced ARDS and a Pao_2/Fio_2 ratio < 150 mm Hg (weak recommendation, moderate quality of evidence). Appropriate sedation and pain control must be maintained while receiving NMBA.
- Conservative fluid strategy should be used for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (strong recommendation, moderate quality of evidence).

Glucose Control

- Begin insulin when 2 consecutive blood glucose measurements exceed 180 mg/dl.
- A protocolized approach to blood glucose management in ICU patients with sepsis should be used, starting insulin dosing when two consecutive blood

glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤ 180 mg/dL rather than an upper target blood glucose level ≤ 110 mg/dL (strong recommendation, high quality of evidence).
- Blood glucose values be monitored every 1 to 2 h until glucose values and insulin infusion rates are stable, then every 4 h thereafter in patients receiving insulin infusions.
- Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values.

Deep Venous Thrombosis (DVT) Prophylaxis

- Low molecular weight heparin (LMWH) should be used for the prevention of DVT (strong recommendation, moderate quality of evidence)
- LMWH rather than UFH should be used for VTE prophylaxis in the absence of contraindications to the use of LMWH (strong recommendation, moderate quality of evidence)
- The combination of heparin pharmacotherapy and pneumatic compression devices (unless contraindicated) for pts. with severe sepsis should be used (weak recommendation, low quality of evidence)
- Mechanical VTE prophylaxis should be used when pharmacologic VTE is contraindicated (weak recommendation, low quality of evidence).

Nutrition

- Parenteral nutrition should not be initiated over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible (strong recommendation, moderate quality of evidence).
- Early initiation of enteral feeding rather than a complete fast or only IV glucose should be started in critically ill patients with sepsis or septic shock who can be fed enterally (weak recommendation, low quality of evidence).
- Early trophic/hypocaloric or early full enteral feeding should be initiated in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance (weak recommendation, moderate quality of evidence).

Corticosteroids

- IV hydrocortisone should not be used to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Renal Replacement Therapy

- RRT can be used in patients with sepsis and acute kidney injury (weak recommendation, moderate quality of evidence) if indications for RRT (hyperkalemia, severe acidemia, fluid overload, etc) exist.
- Continuous therapies might facilitate management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence).

Goals of Care, Communication of Prognosis

Goals of care and the prognosis should be addressed no later than 72 h after admission depending on cultural considerations (weak recommendation, low quality of evidence)

Goals of care should be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (strong recommendation, moderate quality of evidence).

Surviving Sepsis Campaign Recommendation Highlights—See Table 8.2

Table 8.2 Surviving sepsis guidelines 2012 vs. 2016

	2012	2016
Definition	Systemic manifestation of infection + suspected infection Severe sepsis – sepsis + organ dysfunction	Condition of life-threatening organ dysfunction (such as hypotension, altered mentation, oliguria, and others) due to a dysregulated host response to infection (confirmed or suspected)
Initial resuscitation	At least 30 ml/kg in first 3 h Use crystalloid Use albumin if patients require “substantial” fluid	
	Protocolized care including CVP, ScVO2 Normalize lactate	Dynamic resuscitation markers Normalize lactate
Vasopressors	Target MAP > 65 1. Norepinephrine 2. Add epinephrine or vasopressin to achieve target 3. Avoid dopamine	
Steroids	Only for patients in refractory septic shock	
Antibiotics	One or more antibiotics against presumptive pathogen Combination therapy for neutropenic patients and pseudomonas	Initial broad spectrum De-escalate as soon as possible
Source control	Achieve in 12 h	Achieve as soon as possible
Ventilator	Use TV - 6 ml/kg	
		Against HFOV
		Unable to make recommendation on NIV

Key Points

- SOFA and qSOFA increase the speed and precision in the diagnosis of sepsis.
- Administer broad spectrum antibiotics within 1 hour after the diagnosis of sepsis (draw cultures, if possible, before antibiotics are administered).
- Markers of tissue perfusion rather than CVP alone should be used in the assessment of volume resuscitation.
- Routine transfusion of RBC should not be considered for Hgb greater than 7.
- Parenteral nutrition should not be used within the first 7 days in the management of sepsis.
- Goals of care should be discussed with the first 72 h.

Review and Correlation of the Following Guidelines

Sepsis-3 (JAMA 2016; 315(8):801–810)

The Surviving Sepsis Guidelines 2012 (Crit Care Med. 2013;41:580–637)

- Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (Crit Care Med. 2017 doi: 10.1097/CCM.0000000000002255)

Part II
Extended Topics in Hospital Medicine

1.1 Introduction

Driven by quality, readmission rates, and length of stay, research has recently focused on where the best patient care can be delivered and by whom. Specialized units, such as stroke care units, are increasingly being developed. This has driven the contraction of hospital medicine in some areas, while simultaneously expanding its coverage in others. Specialty units can offer highly trained staff advanced care plans, with an emphasis on patient–doctor continuity. It is important that these units demonstrate their effectiveness not only in a theoretical manner but also with data. While their benefits may be obvious, they may also lead to further fragmentation of care. The chapter on stroke units explores these topics.

The benefits of early and effective palliative care continue to be demonstrated. What was once thought of solely as end-of-life care is now integral to the hospitalist approach on many non-life-threatening conditions. The tools and objective measures of this specialty continue to expand, and the chapter in this section covers how palliative care can seamlessly be integrated into hospital medicine.

Hospitalists are often asked to manage both the preoperative clinic and be active in management of the patient in the perioperative phase. In many ways the hospitalist is a natural fit. Research in the area of perioperative medicine continues at a rapid pace and much of it is not known to the practicing hospitalist. The perioperative chapter explores some of the complexities of this field.

Lastly, although not every hospitalist might encounter a patient with obstetric needs, many small community and rural hospitals have hospitalists managing obstetric patients. For this reason, we chose to include a chapter covering first trimester bleeding, and common conditions found among obstetric patients, such as congestive heart failure, asthma, and nausea and vomiting.

Chapter 9
Palliative Medicine

Sonia Malhotra and Robin Ulep

What is Palliative Medicine?

The Center to Advance Palliative Care (CAPC) defines palliative medicine as: "Palliative care, and the medical sub-specialty of palliative medicine, is specialized medical care for people living with serious illness." The goals of palliative medicine are to alleviate the burden of symptoms and improve quality of life for patients and families living with the stress of serious illness. It is provided by an interdisciplinary team consisting of physicians, nurses, social workers, chaplains and others who work collaboratively with a patient's team of specialists to provide an extra layer of support and expertise.

Palliative medicine is appropriate for any age and at any stage in a serious illness and can be provided alongside curative treatment (Fig. 9.1).

The field of palliative medicine has grown in the last two decades with consultative palliative medicine services becoming commonplace in medical settings varying from academic and community hospitals to private clinics. Physicians who consult palliative medicine typically seek support in four domains:

1. Pain and symptom assessment and management
2. Communication between health care teams and patients and/or family regarding goals of care and advanced medical decision making.
3. Provision of support to patients, families, and health care teams involved
4. Hospice services

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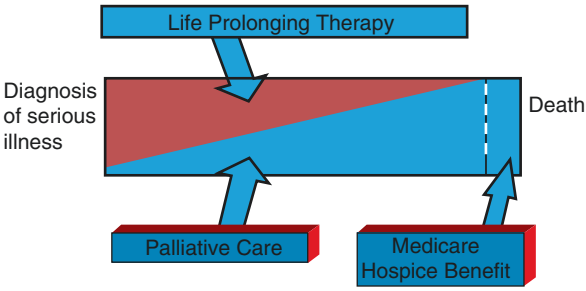


Fig. 9.1 Palliative medicine's role in the course of illness

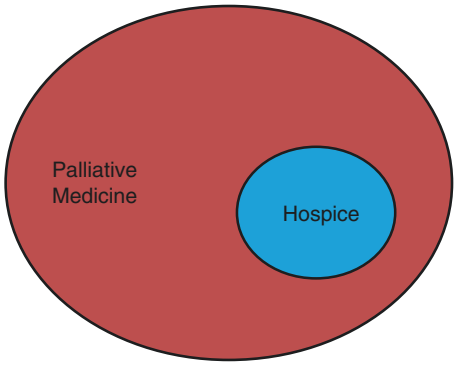


Fig. 9.2 Palliative medicine and hospice care

Palliative medicine has often been thought to be synonymous with hospice or end-of-life care which is simply not the case. Hospice care focuses on keeping patients comfortable who have a prognosis of less than 6 months or those who demonstrate a decline in health. Hospice is a branch of palliative medicine (Fig. 9.2) and a service that palliative medicine teams often help to coordinate and/or provide.

Pain and Symptom Management

Palliative care teams assist with symptom burden associated with serious illness, including (but not limited to) pain, nausea and vomiting, depression and anxiety, loss of appetite, constipation, fatigue, and delirium.

Pain is one of the most common symptoms experienced by patients with life-threatening and chronic illnesses. Treatment plans require clinicians to recognize and assess pain with frequent reevaluation of symptoms and therapies. Clinicians should strive for their patients to be at a tolerable level of pain, not necessarily pain free. When achieving this goal is difficult, early referral to a palliative care physician or pain specialist should occur.

Pain is a subjective feeling and requires a detailed history from the patient and caregiver. Delineating the type of pain a patient is experiencing is imperative as it guides therapy and may aid in determining the underlying etiology. Clinicians should

Table 9.1 Opioid equianalgesia conversions

Medication	Parenteral (mg)	Oral (mg)
Morphine	10	30
Oxycodone	–	20
Hydromorphone	1.5	7.5
Oxymorphone	1	10
Fentanyl	0.1	–

utilize pain assessment tools, expectation for length of pain control required, and the patient's individual pain history to help guide decisions for pain management.

Nociceptive pain is caused by past or ongoing tissue injury that activates pain receptors (nociceptors) in the skin, soft tissue, skeletal muscle, bone and certain viscera to stimulate the pain response. This type of pain is common in cancer and opioids are a mainstay treatment. Clinicians who use opioids should be well versed in equianalgesia conversions (Table 9.1).

Chronic Pain

With the move to make palliative medicine services available earlier in the course of serious illness [1], palliative care clinics will be asked more often to care for patients with chronic pain. This will include patients with more favorable prognoses such as cancer survivorship, HIV, heart failure, and emphysema to name a few. Pain management for these patients is different than those patients with advanced disease and a short prognosis. Acute pain is related to tissue injury and responds to opioid analgesics [2]. Chronic pain, which is pain lasting for greater than 3 months, has been thought to be more related to nervous system changes rather than tissue injury [3].

Core competencies have been developed for palliative medicine providers to manage chronic pain in the outpatient setting [4]. These include: (a) Medical knowledge of psychiatric illness and substance abuse (b) Knowledge of pharmacologic therapies including research indicating limited efficacy of opioids [5, 6] (c) Use of an interdisciplinary team and therapies to help manage chronic pain including the use of non-pharmacologic modalities (d) Communication in an empathetic manner that frames prescribing decisions in a patient-centered manner and relays provider concerns and (e) Practice-based learning to further develop and refine skills.

Communication

Common communication tasks for palliative medicine clinicians include communicating serious news and discussing goals of care. A single family meeting is one part of a series of conversations that patients need to absorb serious news. Several models of patient–doctor communication exist to provide a map for leading these conversations (Tables 9.2 and 9.3). These conversations should be held with any family

Table 9.2 SPIKES model for giving bad news

S Setting	Prepare yourself with the medical facts
P perception	Find out the patient's perception of the medical situation
I invitation	Find out how much information the patient wants to hear
K knowledge	Give information in clear, simple, direct language
E empathize	Respond to patient emotions
S summarize	Summarize the clinical information and make a plan for the next steps

Table 9.3 Ask-tell-ask model for giving bad news

Ask	Ask the patient what their current understanding of their medical course is
Tell	Tell patients information that needs to be communicated (such as bad news or treatment options) in clear, direct, simple language
Ask	Ask the patient for their understanding of the information you gave them

Table 9.4 NURSE mnemonic for statements of verbal empathy

N: Name	Decreases the emotional intensity of the conversation "It sounds like you are frustrated"
U: Understand	Acknowledges the intensity of what the patient and/or family is going through "I can't even begin to imagine what you all are going through"
R: Respect	Praises the patient and/or family's efforts "you have done an amazing job with everything"
S: Support	Aligns the clinician with the patient and/or family "I will do everything I can to help"
E: Explore	Allows more information to be obtained "would you be able to explain what you meant by that?"

members the patient would like included and other clinicians whose presence will assist with the content of the conversation.

(a) *Organizing the Meeting*: Meetings should be planned in advance to ensure inclusion of important components of the patient–doctor relationship [7]. A pre-meeting of all clinicians who will attend the meeting should occur to negotiate roles and discuss prognostic information and treatment options.

(b) *The Start of the Meeting:* The purpose of the meeting and all clinicians involved in it should be introduced at the start of the meeting. Patients should then be asked to explain their perception of the illness and understanding of the clinical course. Prior to providing information, clinicians should ask how much information a patient would like to receive.

(c) *Giving Information:* Clinicians should provide information in small amounts at a basic level of comprehension. The use of medical jargon should be avoided [8]. Frequent pauses should be used to allow the patient to mentally process and verbally respond. Clinicians should expect to respond to the emotion of giving serious news which can be conveyed through verbal empathetic statements (Table 9.4) or non-verbal methods such as touch, nodding, silence, or eye contact.

(d) *Discussing Transitions of Goals of Care or Summarizing the Discussion*: Some patients may be willing to discuss goals of care. Clinicians can obtain this by eliciting concerns, values and goals, balancing realism and hope, and making recommendations. Other patients may prefer to take time to process the serious news given. In this situation, plans should be made for next steps including answering questions the patient or family has, summarizing the conversation, and deciding when to meet next.
(e) *After the Meeting*: Clinicians involved should take time to debrief the meeting and reflect on their own emotions, communication strategies, and challenges encountered during the conversation.

Effective communication strategies are tools to help clinicians better understand the course of a patient's illness. Additionally, these strategies may assist in decreasing physician stress and burnout [9].

Support for Patients, Families, and Providers

Palliative medicine teams are interdisciplinary, consisting of multiple members (Fig. 9.3). All members work collaboratively to provide support to patients, families, and the teams involved in the patient's care. This allows the team to address the emotional, spiritual, social, and financial challenges involved in the care of patients with serious illnesses that may be life-limiting. Families who receive palliative care services earlier feel less angry and less in denial about the anticipated death of their loved one [10]. A positive relationship exists between patient and family satisfaction with care and the quality of communication and support received from patient care teams [11].

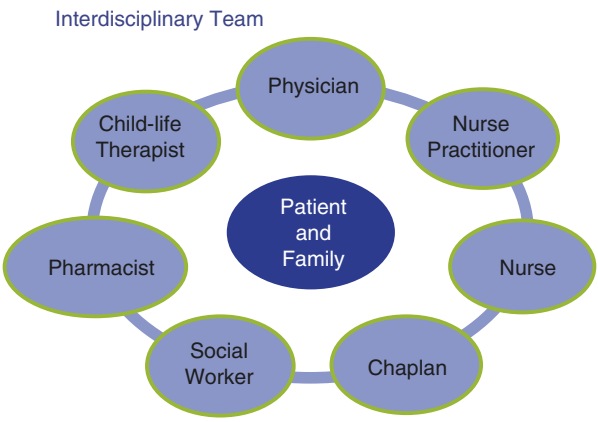


Fig. 9.3 Example of palliative medicine interdisciplinary team

Hospice Care

Hospice care is a model for quality compassionate care that focuses on caring, not curing. It is both a philosophy of care and a regulated insurance benefit through the Medicare Hospice Benefit (MHB). The MHB pays for 85.5% of all hospice care, with the remaining balance paid by Medicaid, private insurance, charity, or the patients themselves. Patients are eligible to receive hospice care under the MHB if they meet the following criteria: (1) Life expectancy certified by two physicians to be 6 months or less and (2) Forgoing ongoing therapy or curative medical treatment related to the terminal diagnosis.

Approximately 1.6 to 1.7 million patients used hospice services in 2014 and that estimate is steadily increasing [12]. This includes patients who died while in hospice care, those who received care in 2013 and continued to receive care in 2014 (known as "carryovers"), and those who left hospice care in 2014 to pursue curative treatment or had extended prognoses (known as "live discharges").

Hospices must be certified by Medicare and be in compliance with the Hospice Conditions of Participation (CoP) for patients to receive services under the MHB [8, 13–17]. Services provided by hospice are divided into core and noncore services [8, 13–17]. (Table 9.5).

Hospice can be classified into home-based care and inpatient care.

(a) *Home-based care*: Includes routine home hospice and continuous home care. Routine home hospice is the most common type, serving approximately 93.8% of all hospice patients [12]. This type of care includes hospice services provided in a private home, nursing home, or residential facility. In comparison, continuous home care is for hospice patients who qualify for inpatient care, but desire to remain at home. It is an alternative to support the patient and their caregiver through brief periods of crisis.
(b) *Inpatient care*: Includes general inpatient care or short-term respite care. General inpatient hospice care is provided at an acute care unit or facility where

Table 9.5 Core and noncore hospice services

Core hospice services	Noncore services
Skilled nursing services	Physical therapy
Physician services	Occupational therapy
Volunteer services	Speech-language pathology
Counseling services (including bereavement counseling)	Home health care
Spiritual care	Homemaker services
Dietary counseling	Administration of drugs and medical supplies
Social services	Continuous home care
	Respite care

intensive nursing and psychosocial support is available outside of the home. Inpatient hospice stays are for acute, uncontrolled, complex symptom management that cannot be managed in the home setting. Medicare payment rules limit the number of patient care days that occur outside of a patient's residence to ensure that hospice care under the MHB remains a home delivery model [8, 13–17].

Respite care is limited to 5 consecutive days of inpatient hospice management as an effort to relieve and alleviate caregivers for brief periods of time. Utilization of respite care often occurs when caregivers need to travel or tend to their own health needs. Respite care can be provided by the hospice agency in a variety of contracted settings such as the inpatient hospice facility, at a hospital, or in a local nursing home.

Often patients and families enroll in hospice too late in the course of their disease to use the hospice benefit fully. The median length of stay for patients in hospice during the year 2014 was 17.4 days, while one third of patients who enrolled in hospice died within 1 week of enrollment [12]. Barriers to hospice being provided in a timely manner include the uncertainty of prognosis, availability of more complex treatment options, hospice admission criteria, and lack of knowledge of hospice services [18]. Development of home palliative medicine programs and enrollment of patients in them may assist in bridging some of these barriers.

What Are the Benefits of Palliative Medicine?

Palliative medicine services have traditionally been used late in the course of a patient's disease. There is large potential to improve the quality of life and reduce the costs associated with the use of medical services if palliative medicine is provided earlier as part of the continuum of care.

Across hospital programs of varying sizes in the United States, palliative care services have a mean penetration of 4.4%. This is an increase of 63% since 2008. Nationwide, palliative medicine is primarily an inpatient consult service with a growing number of programs offering an inpatient palliative care unit and outpatient clinics [19]. Over the past 8 years, hospital palliative care programs have increased consult volumes by 91% from a mean of 425 total consults in 2008 to 819 total consults in 2014. Hospitalists refer patients to palliative medicine most commonly (Figs. 9.4, 9.5, 9.6, and 9.7).

The most common diagnosis for palliative medicine consultation is cancer (25.9%). Steadily increasing numbers of consults are being seen for patients with cardiac (10.4%), pulmonary (10.4%), and neurological diseases (8.7%) [19].

Palliative medicine assists in the reduction of hospital costs by offering customized and intensive services to a small yet high-cost proportion of patients. Research

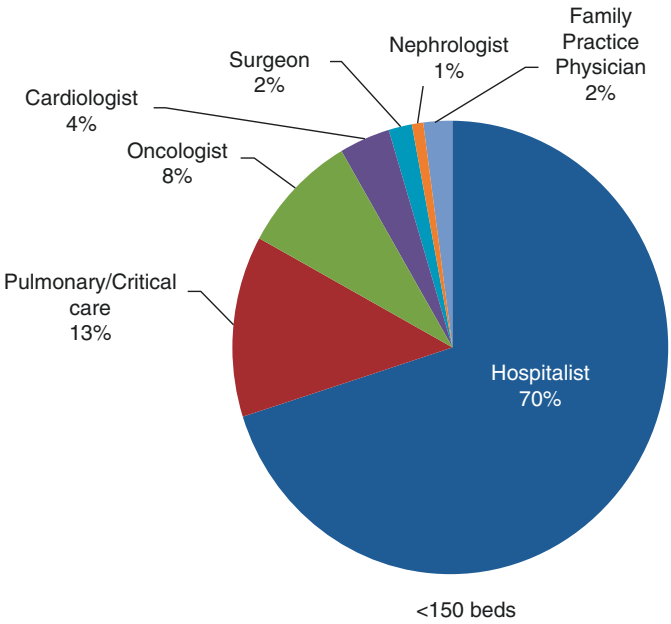
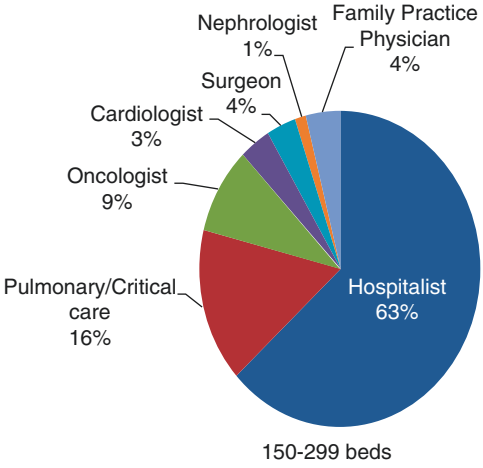


Fig. 9.4 Referral percentages per specialty and hospital size (<150 bed hospitals)

Fig. 9.5 Referral percentages per specialty and hospital size (150–299 bed hospitals)



has demonstrated that palliative care consultation reduced hospital costs by $1700 per admission for patients discharged alive and approximately $5000 per admission for patients who died [20]. Early palliative care consultation can reduce the cost of hospital stays for patients admitted with advanced cancer diagnoses by up to 24%. Additional studies suggest that patients with early palliative care consultation are more likely to receive care outside of the ICU, are less likely to be hospitalized repeatedly, and enroll in hospice earlier [21].

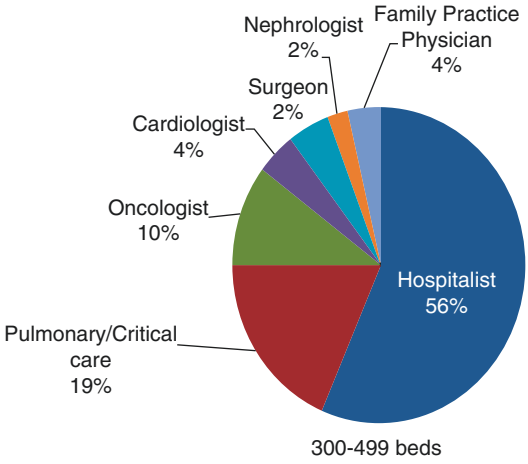


Fig. 9.6 Referral percentages per specialty and hospital size (300–499 bed hospitals)

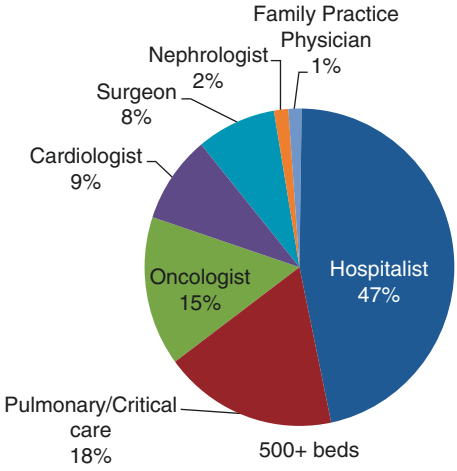


Fig. 9.7 Referral percentages per specialty and hospital size (500+ bed hospitals)

In addition to cost savings, palliative medicine consultation improves quality of life through alleviation of symptom burden. This was most effectively seen in a study that looked at patients with metastatic non-small-cell lung cancer [22]. Patients were randomized in two groups looking at standard oncologic care versus standard oncologic care and the integration of outpatient palliative medicine consultation and follow-up visits. Primary outcomes demonstrated improvement in quality of life scores, anxiety screening scores, and depression screening scores (Fig. 9.8). A secondary outcome of improved survival was noted in the group receiving standard care with palliative care (median survival 11.6 vs. 8.9 months; $p = 0.02$) (Fig. 9.9). Results also showed that the palliative care patients had less aggressive end-of-life care and increased documentation of resuscitation preference.

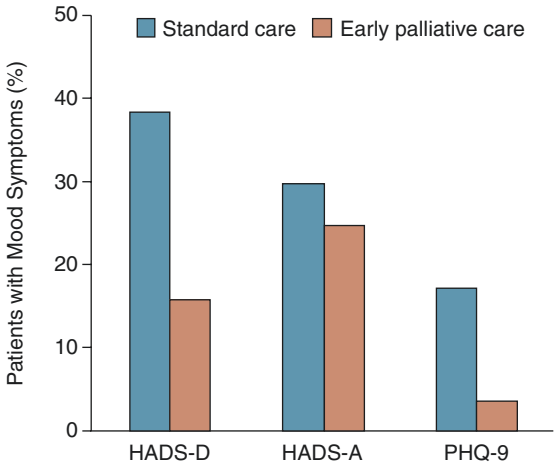


Fig. 9.8 Depression and anxiety screening scores in standard care vs palliative care patients [22]

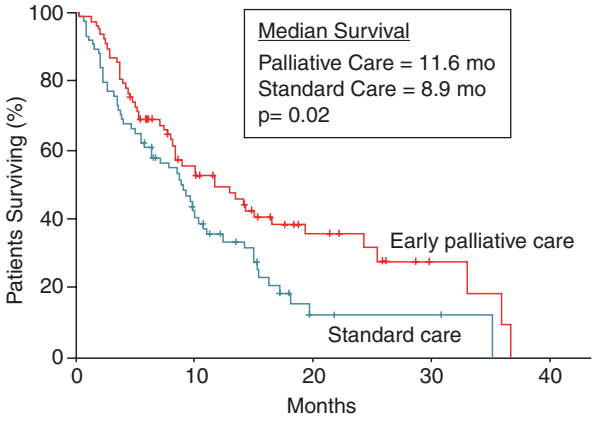


Fig. 9.9 Survival in standard care vs palliative care patients [22]

Conclusion

The goals of palliative care are to achieve quality of life and alleviate suffering through pain and symptom management, communication regarding disease progression and goals of care, and support of patient and family values. It assists in guiding patients and families through the struggles of serious, life-limiting illnesses. Palliative medicine can be provided in various settings and has demonstrated reductions in the cost of care while providing high quality of care.

Key Points

- Palliative medicine is a continuum of care and should be provided early in the course of a serious illness
- Hospice is a branch of what palliative medicine clinicians and teams are able to provide

- Pain is one of the many symptoms palliative medicine clinicians can assist in managing to improve patients' quality of life
- Communication skills are essential for palliative medicine clinicians and require specific strategies to address patient illness
- Palliative medicine reduces cost of care while providing high quality care

References

1. Beresford L, Meieir D. Outpatient clinics are a new frontier for palliative care. J Palliat Med. 2008;11(6):823–8.
2. Portenoy R, Forbes K, Lussier D, et al. Difficult pain problems: an integrated approach. In: Doyle D, Hanks G, Cherny N, Calman K, editors. Oxford textbook of palliative medicine. New York: Oxford Univeristy Press; 2005.
3. Griffis CA. Neuroimmune activation and chronic pain. AANA J. 2011;79(1):31–7.
4. Merlin JS, Childers J, Arnold RA. Chronic pain in the outpatient palliative care clinic. Am J Hosp Palliat Med. 2012;30(2):197–203.
5. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta analysis of effectiveness and side effects. CMAJ. 2006;174(11):1589–94.
6. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010;20(1):CD006605.
7. Smith RC, Hoppe RB. The patient's story: integrating the patient- and physician-centered approaches to interviewing. Ann Intern Med. 1991;115(6):470–7.
8. Chapman K, Abraham C, Jenkins V, et al. Lay understanding of terms used in cancer consultations. Psychooncology. 2003;12(6):557–66.
9. Graham J, Potts HW, Ramirez AJ. Stress and burnout in doctors. Lancet. 2002;360:1975–6.
10. Kim SH, Hwang IC, Ko KD, et al. Association between the emotional status of family caregivers and length of stay in a palliative care unit: A retrospective study. Palliat Support Care. 2015;13(6):1695–700. doi:10.1017/S1478951515000619. Epub 2015 Jun 11.
11. Holland JM, Keene JR, Kirkendall A, Luna N. Family evaluation of hospice care: examining direct and indirect associations with overall satisfaction and caregiver confidence. Palliat Support Care. 2015;13(4):901–8.
12. National Hospice and Palliative Care Organization. Facts and Figures: Hospice Care in America. Alexandria, VA; 2015. http://www.nhpco.org/sites/default/files/public/Statistics_Research/2015_Facts_Figures.pdf. Accessed 15 Aug 2016.
13. Centers for Medicare & Medicaid Services. Medicare and Medicaid Programs: Hospice Conditions of Participation: Final Rule, Code of Federal Regulations 42CFR418.50-100, Conditions of Participation. 2002.
14. Centers for Medicare & Medicaid Services. Medicare and Medicaid Programs: Hospice Conditions of Participation: Final Rule, Code of Federal Regulations 42CFR418.64, Core Services. 2002.
15. Centers for Medicare & Medicaid Services. Medicare and Medicaid Programs: Hospice Conditions of Participation: Final Rule, Code of Federal Regulations 42CFR418.302 Payment Procedures for Hospice Care. 2002.
16. Centers for Medicare & Medicaid Services. Medicare and Medicaid Programs: Hospice Conditions of Participation: Final Rule, Code of Federal Regulations 42CFR418.70-78 Furnishing of Non-Core Services. 2002.
17. Centers for Medicare & Medicaid Services. Medicare and Medicaid Programs: Hospice Conditions of Participation: Final Rule, Code of Federal Regulations 42CFR418.204(b) Special Coverage Requirements. 2010.
18. James N, Field D. The routinization of hospice: charisma and bureaucratization. Soc Sci Med. 1992;34:1363–75.

19. Center to advance palliative care and national palliative care research center. national palliative care registry. New York, NY; 2015. https://registry.capc.org/metrics-resources/summary-data/. Accessed 15 Aug 2016.
20. Morrison RS, Penrod JD, Cassel JB, et al. Cost savings associated with US hospital palliative care consultation programs. Arch Intern Med. 2008;168(16):1783–90.
21. Morrison RS, Dietrick J, Ladwig S, et al. Palliative care consultation teams cut hospital costs for Medicaid beneficiaries. Health Aff (Millwood). 2011;30(3):454–63.
22. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363:733–42.

Chapter 10
Stroke Units and Their Effect on Patient Outcomes

Gabriel Vidal and Tara von Kleist

Introduction

Stroke is the fifth-leading cause of death, and is the leading cause of long-term and preventable disability in the United States (www.strokeassociation.org). Each year around 795,000 people experience a stroke in the US, an average of one stroke every 40 s. It is a costly disease with an estimated yearly expense of $33 billion [1]. It is expected that the burden of stroke will only continue to grow in the future due to the steady growth of the aging population in the United States.

Recently, there has been an emphasis on improving stroke care with the goal of bettering outcomes and reducing disease mortality. The most recognized efforts in the US include the development of stroke systems of care, with emphasis on the acute treatment and the evolution and proliferation of stroke centers among the country. Stroke centers vary in the level of services provided, but acute care remains one of the most integral components of any center. Stroke unit is a term that describes a specialized multidisciplinary care approach which focuses on the care of stroke patients in a dedicated ward. This chapter will include a review of the components and various types of stroke units, the pitfalls and difficulties in establishing a stroke unit, and what may be the future of stroke units with the advent of new technological solutions.

Acute Stroke Care

It is important to understand that the most beneficial intervention for a stroke patient is stroke prevention. Risk factor modification can not only decrease the chances of stroke but of recurrent strokes as well (Table 10.1). The yearly rate of recurrence

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Table 10.1 Modifiable and non-modifiable risk factors for stroke

Stroke risk factors	
Modifiable	Not-modifiable
Hypertension	Age
Diabetes	Gender
High cholesterol	Race
Smoking	Hereditary conditions
Atrial fibrillation	Prior stroke
Carotid artery disease	
Tobacco use	
Physical inactivity	
Obesity	
Excessive alcohol	
Illicit drug use	

after a stroke or transient ischemic attack is estimated to be about 3–4%, which is half that of in the 1960s due to improvements in blood pressure control and increasing use of antiplatelets [2]. Unfortunately, not all risk factors are modifiable, but aggressive management can help avoid cerebrovascular disease.

Once a stroke is recognized, access to early treatment is extremely important. To highlight this, it is estimated that 1.9 million neurons are lost every minute that a stroke goes untreated [3]. That means every hour, the brain loses the equivalent number of neurons as 3.6 years of aging [3]. Reperfusion is shown effective in reducing the likelihood of disability and death, but is time sensitive. The use of IV tPA is the gold standard since the NINDS IV tPA trial was completed in the mid-1990s, which showed improvement in outcomes of eligible patients only if initiated within 3 h of the onset of symptoms [4]. However, more recently, it was demonstrated that there may be some benefit for selected patients when given up to 4.5 h from onset of symptoms [5].

Endovascular treatment with thrombectomy for acute stroke is the most current therapy with demonstrable effective results. Only a small percentage of patients with acute ischemic strokes will benefit from this intervention, making correct patient selection crucial. The principle of the therapy lies in the removal of the blockage (thrombectomy) causing the stroke, but this is possibly only if the vessel is large enough for access with a catheter. Also, this must be accomplished before brain tissue suffers irreparable damage.

A recent publication reviewed and analyzed the combined data from five randomized clinical trials to evaluate endovascular care versus standard medical care for patients with acute ischemic stroke due to large vessel occlusions. The review concluded that endovascular thrombectomy benefits most patients with acute ischemic stroke secondary to occlusion of the proximal segments of the anterior circulation, irrespective of patient characteristics or geographical location [6]. The review data reported that endovascular thrombectomy led to significantly reduced disability at 90 days when compared with control (adjusted cOR 2.49, 95% CI 1.76–3.53; $p < 0.0001$) [6], and that the number needed to treat with endovascular

Table 10.2 Modified Rankin Scale [7]

Modified Rankin Scale (mRS)	
0	No symptoms
1	No significant disability despite having symptoms; able to perform all usual duties and activities
2	Slight/mild disability; unable to carry out all previous activities, but still able to look after own affairs without assistance
3	Moderate disability; requiring some help, but still able to walk without assistance
4	Moderately severe disability; unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

thrombectomy to reduce disability by at least one level on the modified Ranking Scale (Table 10.2) for one patient was 2.6 [6]. In addition there was no increase in mortality or hemorrhage when compared to patients receiving standard care.

As described previously, not all stroke patients are eligible for acute interventions but most require further comprehensive care in order to optimize their outcomes. They require specialized physicians, therapists, and nurses in order to identify and manage issues to maximize their recovery potential, which stroke units aim to accomplish. According to the Stroke Unit Trialist's Collaboration, the concept of stroke units has been a topic of discussion for over 25 years [8]. Prior to the development of comprehensive and specialized stroke units, patients with strokes who were admitted to a hospital were cared for in internal medicine wards, as part of the general population, with consultations to neurology for management. As neurologic care became specialized, a more focused approach developed, in which stroke patients were grouped together. This unit then provided specialized, multidisciplinary care for this patient population with the goal of improving outcomes.

Stroke Unit Components

After a patient receives acute care for their stroke, whether that involves thrombolysis, endovascular intervention or neither, they would ideally be admitted to a stroke unit in order to optimize their care. A successful Stroke Unit should have certain basic resources to achieve the best care, but there is some degree of variability across the US. In general, a stroke unit requires specially trained staff, specific skills, and resources (Table 10.3) and is ideally associated with institutional resources and services necessary for optimal function (Table 10.4) [8]. This multidisciplinary team cares for stroke patients in a designated ward, rather than a general medical ward that lacks staff trained in stroke care or necessary protocols.

Table 10.3 Specialized personnel and resources essential for a stroke unit

Stroke unit—essential staff and human resources	
Physician	Specialty trained (neurologist, vascular neurologist/neuro-intensivists) 24/7 coverage/availability—Internal medicine support for medical issues
Fellows/residents/advanced practitioners	Supporting physician
Nursing	Nursing training and expertise in stroke care
Social worker/case manager	Knowledge and training in the burden and special circumstances of stroke patients and families
Rehabilitation team	Physical/occupational/speech therapy teams trained and dedicated to the special needs of stroke patients and their rehabilitation
Physical therapy resources	Inpatient facilities available for continued rehabilitation when appropriate once discharged
Community resources	Interactions with community institutions that provide skilled nursing and outpatient/home rehabilitation services to coordinate care of patients after hospitalization. Also active participation in community outreach activities for general population education on stroke care and prevention
Multidisciplinary team meetings	Integrated communications between physicians, therapists, and social work/case managers to better understand and optimize patient needs
Continuous education and training	For both patient and families as well as for the entire multidisciplinary staff who cares for this patient population

Table 10.4 Hospital resources that will optimize stroke unit care

Stroke unit—hospital resources	
Dedicated space	Telemetry capable unit
Advanced imaging	CT, MRI, ultrasound, cervicocerebral angiography, echocardiography
Specialty services	Emergency department, cardiology, vascular surgery, neurosurgery, intensive care/Neurocritical care, radiology, clinical laboratory, physical medicine and rehabilitation
Outpatient clinic support	Follow-up and referrals
Performance improvement	Stroke coordinator

The Stroke Unit Trialist's Collaboration aimed to assess the impact of stroke unit care versus alternative care and identified a hierarchy of care for stroke patients, from inpatient stroke wards to mobile stroke teams. Rehabilitation stroke units as well as comprehensive stroke units which combined acute care with longer term rehabilitation were recognized to be on a spectrum of stroke unit care. Although these varying environments involved care at different stages of stroke recovery, they all involved medical professionals specially trained in stroke, caring for patients in a ward dedicated to stroke.

Stroke Centers

In the past decade, a larger systems based approach has been formed as care for stroke patients was found to still be suboptimal despite the focused management on stroke units. In 2000, a survey of all hospitals in North Carolina found that only 52% of the population resided in a county with basic services (emergency department, brain CT, treatment with tPA, transthoracic echocardiography, carotid ultrasonography, cerebral angiography, carotid endarterectomy) and only 26% with advanced services (basic plus brain MRI, MR angiography, transesophageal echocardiography, transcranial Doppler ultrasonography, interventional radiology) [9]. Additionally, only a small percentage of eligible patients with ischemic stroke were being treated with tPA, despite FDA approval and a 11–13% increase in patients with minimal or no deficits compared with placebo [10]. With this, the Brain Attack Coalition (BAC), a multidisciplinary group of professionals involved in the management of stroke, created recommendations to improve patient care on a systems level. They determined that in order to optimize care for stroke patients, two levels of stroke centers needed to be established—primary and comprehensive [11].

The BAC performed an extensive literature review and identified key elements to incorporate into both primary and comprehensive stroke centers, which had proven to be beneficial. These recommendations included a dedicated stroke unit, as well as written stroke care protocols and access to neuroimaging. For comprehensive stroke centers, recommendations included more specialized services (e.g., vascular surgery, interventional physicians, critical care and staff stroke nurses), advanced imaging and 24 h. access to endovascular and surgical intervention as well as ICU and stroke units [12]. Though these reports highlighted many characteristics important for improved patient outcomes, they really emphasized the importance of stroke units in the care of this patient population [11, 12]. Guidelines were then formed by the Joint Commission based on these recommendations, and there are now over 1000 primary stroke centers and over 100 comprehensive stroke centers with certification in the US.

Stroke Unit Outcomes

Multiple publications have described results from different stroke units and centers as they relate to death, dependence and institutionalization, among others. The review by the Stroke Unit Trialist's Collaboration reported that when patients were cared for in an organized stroke unit, compared to alternative services, there was a significant reduction in the odds of the patient dying or requiring long-term institutional care (OR 0.76, 95% CI 0.67–0.86; $P = 0.0001$) [8]. It also reported that there was a significant reduction of the combined adverse outcomes of death or dependency when compared to alternative services (OR 0.80, 95% CI 0.67–0.97; $P < 0.00001$) [8].

The policy statement from the American Heart Association/American Stroke Association on Interactions within Stroke Systems of Care also supports that hospitals with high stroke volumes and stroke units have better stroke outcomes than hospitals without this expertise [13]. This organization of care is not unique to the US, with variations on the stroke unit described above existing throughout the world. One study from Europe showed an estimated 25% reduction in the risk of death in stroke units [14], and a study from Japan showed reduced risk of in-hospital mortality for both ischemic (3.6 vs 5.7%) and hemorrhagic stroke (14.8 vs 24.1%) for stroke units when compared to alternative care [15].

As stroke units have proven to be beneficial for patient outcomes, many studies around the world have shown a significant benefit for patients when cared for in a Primary or Comprehensive stroke center. Researchers in Finland performed an observational study of over 60,000 patients with ischemic stroke cared for in over 300 hospitals which were divided into Comprehensive or Primary stroke centers or General Hospital based on the publication by BAC [16]. They found a statistically significant reduction in 1 year case-fatality when stroke patients were cared for both at CSC and PSC compared to general hospitals (16% and 11% respectively) [16]. They also found that 1 year after a stroke, patients treated in a stroke center were less likely to be institutionalized and more likely to be living at home [16]. Numerous other studies performed throughout Europe also showed varying degrees of improved mortality, reduced institutionalization and death for patients in stroke units, though their definitions of "stroke unit" were not all identical [14, 17, 18].

Since the certification of designated Stroke Centers, there has been an increase in use of thrombolysis for management of acute stroke among these centers compared to non-stroke centers. As discussed above, the NINDS IV tPA trial was completed in the 1990s providing the foundation for guidelines regarding thrombolysis if eligible. The use of IV tPA remained low despite this until the advent of stroke centers with specialized stroke units for close monitoring, with one study in New York showing an increase by 2.2% [19].

There is less evidence for outcomes related to hemorrhagic stroke, though a study of hospitals in New Jersey including Comprehensive and Primary stroke centers and non-Stroke centers showed that surgical interventions were more likely to occur at CSCs. There was also reduced mortality for this population both in-hospital and up to 1 year after their stroke [20]. Although this is encouraging for the continued development of certified stroke centers, this does not emphasize the use of stroke units specifically in the care for hemorrhagic stroke. Rather it demonstrates the benefits of organizing stroke care at the systems level.

The Future of Stroke Units

A statement by the American Heart Association/American Stroke Association estimated that with the aging population, the prevalence of stroke is expected to increase [20]. This translates to an increase of approximately 3.4 million more people

affected with stroke by 2030, relative to 2012. Simultaneously, the total direct medical stroke-related costs are projected to triple from $71.55 billion in 2012, to $184.13 billion in [21, 22]. Thus it is crucial that proven therapies and care techniques are implemented now, to help control the morbidity and mortality related to stroke. Compounding the problem, is a shortage of vascular neurologists in the US. Some estimates suggest an average of 717 strokes per vascular neurologist per year in the United States. This disparity of supply and demand is more pronounced in rural and underserved urban areas [23].

An area of improvement in care is the use of telemedicine to provide the expertise of vascular neurologist to underserved areas. This would allow vascular neurologists to deliver virtual guidance and expert care for stroke patients, while under the direct care of a non-specialized physician. The pitfalls of this process include the loss of the subtleties of the neurologic examination, as well as the direct impact that face-to-face encounters can provide to patients and their families. However, this still remains an excellent option for those in rural and underserved areas.

The exact date when telecommunications first were used in healthcare is unknown. The first reported complete telemedicine system linking paraprofessionals and physician–patient encounters settings was installed in 1967, linking Logan Airport in Boston to Massachusetts General Hospital [24].

Telemedicine for the management of acute stroke has been active for over 2 decades and multiple studies have demonstrated its efficacy in diagnosing acute stroke, increasing the use of approved therapies, improving long-term outcomes and being a cost-effective alternative in the long term [24]. It has overcome geographical barriers to stroke care and allowed earlier treatment of patients.

Despite being effective for the diagnosis and management of acute stroke, telemedicine has not been fully exploited for immediate post-acute stroke care. A "virtual provider" may not be the final solution to the problem of lack of availability of experts in the field of stroke care, but it does provide an opportunity to bring specialized care to underserved areas. Acute care is only one component of the multiple disciplines that are the hallmark of management of these patients. Once the diagnosis is established, a meticulous workup usually follows in a stroke unit, aimed at determining the etiology of the event so that an optimal medical therapy can be established, tailored to each individual patient's needs.

Different stroke syndromes and etiologies can be misdiagnosed by untrained providers, leading to an increase in the recurrence of future events, and resulting in suboptimal therapies that may otherwise lead to better outcomes. Vascular neurologist availability would lead to better diagnosis, radiographic interpretation, and treatment for stroke patients. With the aid of ancillary staff and under the supervision of non-specialized physicians, telemedicine may be a vehicle to bring the expertise of a vascular neurologist to a remote stroke unit, thus linking the resources of a stroke center to a hospital without the desired resources. It would allow for other members of the care team to provide their services remotely as well. At the same time, it would reduce the number of transfers of patients into tertiary centers, hence maintaining patients close to home, their families, and their support system (Figs. 10.1 and 10.2).

Fig. 10.1 Cover of 1924 Radio News magazine, foreshadowing the use of telemedicine to treat patients remotely

Fig. 10.2 An example of modern telemedicine care

Conclusion

As the population continues to age, the prevalence of stroke will do the same despite best efforts at primary prevention. Developing initiatives and therapies that help decrease the burden of stroke are more important now than ever. Along with the innovations in acute stroke care, stroke units are an invaluable tool to help reduce such burden. Caring of patients with strokes in a stroke unit and providing specialized care provides an optimal environment for high performance and the opportunity to keep morbidity, mortality, and long-term institutionalization to a minimum.

The stroke unit model has demonstrated that it helps improve the outcomes of stroke patients and increases the odds for patients to have independence after a stroke and survive it when compared to less organized services. Despite such results, institutions are required to provide a large number of resources to make them function optimally. Alternatives for areas with fewer resources, like telemedicine, seem to be an adequate option that allows expert care to be provided across larger territories and to more patients, ultimately bringing elements of the stroke unit to the patient.

Key Points

- After acute treatment, stroke patients require specialized and coordinated care in order to identify their needs and facilitate maximal recovery
- Stroke units involve a multidisciplinary approach to the care of stroke patients and have led to the development of Stroke Centers
- Stroke units reduce mortality and improve outcomes of stroke patients when compared with non-specialized care
- Stroke units require an institutional commitment as they require a large number of resources to function optimally
- Telemedicine may impact the post-acute stroke care in the near future, allowing specialized care to reach underserved areas

References

1. Mozaffarian D, Benjamin E, Go A, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation. 2016;133(4):38–360.
2. Hong KS, Yegiaian S, Lee M, Lee J, Saver JL. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. Circulation. 2011;123:2111–9.
3. Saver JL. Time is brain—quantified. Stroke. 2006;37(1):263–6.
4. NINDS. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med. 1995;333(24):1581–7.

5. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–29.
6. Goyal M, Menon B, van Zwam W, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723–31.
7. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957;2(5):200–15.
8. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2013;9(9):CD000197.
9. Goldstein B, Hey A, Laney R. North Carolina stroke prevention and treatment facilities survey. Statewide Availability of Programs and Services. Stroke. 2000;31(1):66-70.
10. Alberts J. tPA in acute ischemic stroke: United States experience and issues for the future. Neurology. 1998;51:S53–S5.
11. Alberts J, Hademenos G, Latchaw E, Jagoda A, Marler R, Mayberg R, et al. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. JAMA. 2000;283:3103–9.
12. Alberts J, Latchaw E, Selman R, Shephard T, Hadley N, Brass M, et al. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. Stroke. 2005;36(7):1597–616.
13. Higashida R, Alberts J, Alexander N, Crocco J, Demaerschalk M, Derdeyn P, Goldstein B, Jauch C, Mayer A, Meltzer M, Peterson D. Interactions within stroke systems of care a policy statement from the American Heart Association/American Stroke Association. Stroke. 2013;44(10):2961–84.
14. Rudd G, Hoffman A, Irwin P, Lowe D, Pearson G. Stroke unit care and outcome results from the 2001 National Sentinel Audit of Stroke (England, Wales, and Northern Ireland). Stroke. 2005;36(1):103–6.
15. Inoue T, Fushimi K. Stroke care units versus general medical wards for acute management of stroke in Japan. Stroke. 2013;44(11):3142–7.
16. Meretoja A, Roine O, Kaste M, Linna M, Roine S, Juntunen M, Erilä T, Hillbom M, Marttila R, Rissanen A, Sivenius J. Effectiveness of primary and comprehensive stroke centers PERFECT stroke: a nationwide observational study from Finland. Stroke. 2010;41(6):1102–7.
17. Bersano A, Candelise L, Sterzi R, Micieli G, Gattinoni M, Morabito A, PROSIT Study Group. Stroke Unit care in Italy. Results from PROSIT (Project on Stroke Services in Italy). A nationwide study. Neurol Sci. 2006;27(5):332–9.
18. Terent A, Asplund K, Farahmand B, Henriksson M, Norrving B, Stegmayr B, Wester PO, Åsberg KH, Åsberg S. Stroke unit care revisited: who benefits the most? A cohort study of 105 043 patients in Riks-Stroke, the Swedish Stroke register. J Neurol Neurosurg Psychiatry. 2009;80(8):881–7.
19. Xian Y, Holloway G, Chan S, Noyes K, Shah N, Ting H, Friedman B. Association between stroke center hospitalization for acute ischemic stroke and mortality. JAMA. 2011;305(4):373–80.
20. McKinney S, Cheng Q, Rybinnik I, Kostis B. Comprehensive stroke centers may be associated with improved survival in hemorrhagic stroke. J Am Heart Assoc. 2015;4(5):e001448.
21. Ovbiagele B, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. Stroke. 2013;44(8):2361–75.
22. Gupta R. Reappraisal of stroke systems of care. J Neurointerv Surg. 2016;8(8):767.
23. Leira C, et al. The growing shortage of vascular neurologists in the era of health reform: planning is brain! Stroke. 2013;44(3):822–7.
24. Zundel K. Telemedicine: history, applications, and impact on librarianship. Bull Med Libr Assoc. 1996;84(1):71–9.

Chapter 11
Update in Perioperative Medicine: Updates, Advances, Controversies in Perioperative Care

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Introduction

This chapter gives an introduction to preoperative evaluation, with an emphasis on risk assessment, optimization of preexisting medical conditions, and an analysis of complication prediction based on various models. It also presents efforts directed towards prevention of anticipated complications and introduction of novel concepts in perioperative care. It explores the expanding role of the hospitalist in this process and what tools are currently available.

Perioperative care involves care of the patient around the time of surgery. The various phases of the perioperative care include preoperative, intraoperative, and the postoperative period.

Dedicated preoperative evaluation clinics offer multiple proven benefits for the care of the surgical patient. A focus on risk assessment and coordination of the care with the surgeon has resulted in improved quality. Enhanced perioperative care has been shown to reduce preoperative testing, reduce day of surgery cancellations and optimization of operating room time [1]. In addition subspecialty consultation and overall costs have been reduced.

Hospitalists in the Perioperative Care

Preoperative evaluation is provided by a variety of specialist including anesthesiologists, surgeons, primary care physicians, and hospitalists.

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Having experience in Inpatient Medicine and an increasing role in surgical co-management, hospitalists have expectedly been involved in the pre-, post-, and perioperative phases of care of the surgical patient. They may serve as primary attending or as consultants during the patient's stay in the hospital. They are called upon to address the patient's medical conditions and facilitate effective discharge planning.

Traditionally, preoperative assessment and the preoperative clinic has been managed and staffed by anesthesiologists. Hospitalists are also finding roles in the preoperative clinics as both consultants and directors. Their skills are particularly useful in the management of medically complex patients, where in conjunction with anesthesiologists they have been proven to improve perioperative outcomes [2].

Preoperative Clinic: Function Overview

The focus of preoperative evaluation is to perform comprehensive evaluation of the patient. This includes assessing risk and mitigation. Risk assessment takes into account the interaction of anesthesia type, patient, and surgery specific factors. Anesthetic factors include the type of anesthesia such as general or neuroaxial. Surgical factors include the type, extent, and duration of surgery. Patient factors include age, comorbidities, and lifestyle. Various risk prediction models are available for risk assessment of postoperative complications. Some of the models are organ specific such as the revised cardiac risk factor index (RCRI) for cardiac risk assessment and some refer to post-op complications in general such as the American society of Anesthesiologists Physical Status Classification (ASA), based on the presence and severity of preexisting systemic disease.

Preoperative evaluation should also focus on the adequacy of control of underlying chronic medical conditions such as diabetes mellitus, hypertension, chronic kidney, lung, and heart diseases. If those conditions are felt to be uncontrolled, efforts directed towards optimizing them should take place prior to surgery.

Another aspect of perioperative care is to anticipate potential postoperative complications. Some perioperative medical complications are predictable based on the patient's preexisting medical conditions. These include the delirium risk in patients with dementia and acute kidney injury risk in patients with advanced chronic kidney disease. Strategies to reduce complications postoperatively continue to be developed. Being aware of the potential complications will enable the perioperative care team to initiate protocols that lead to earlier diagnosis and improve outcomes.

Preoperative evaluation may occur in the hospital (often emergent, semi elective surgery) or ideally in an outpatient setting, which determines the time available for optimizing the patient prior to surgery.

During the preoperative evaluation process, there has been an evolution from simply providing clearance for surgery and anesthesia to the more useful risk stratification process (high, intermediate, and low risk for complications). With this information, informed decisions can be made by the surgical and anesthesiology

team. For instance, if the patient was felt to be at high risk for surgery, the surgeon may plan a less invasive procedure. Risk assessment can also assist the patient in making an informed decision concerning the risk and benefits of the procedure. Risk assessment may also be beneficial in developing care plans for the patient in the perioperative period.

Estimating Perioperative Cardiac Risk

Many patients undergoing major noncardiac surgery are at risk of having an adverse cardiac event in the perioperative period. Various risk evaluation models are available to estimate perioperative cardiac risk.

Risk assessment models in patients undergoing noncardiac surgery include the following: the Revised Cardiac Risk Index (RCRI) which has been widely used and validated [3]. Other models are the American College of Surgeons National Surgical Quality Improvement Program risk (ACS-NSQUIP) [4], and the myocardial infarction and risk calculator (MICA NSQUIP) database risk model.

Preoperative cardiac evaluation involves obtaining a history of preexisting heart disease including coronary artery disease, heart failure, valvular disease, and arrhythmias. A history of related vascular disease is also obtained including cerebrovascular disease, renal disease, and diabetes mellitus. A focused cardiovascular exam should be performed. An assessment should also be made for stability of the preexisting cardiac conditions or the presence of new onset acute cardiac conditions. This includes the presence of unstable coronary syndromes or decompensated heart failure. Cardiac risk also depends on the surgery, with higher risk seen for certain surgeries such as vascular, open intraperitoneal, or intrathoracic.

Functional status needs to be determined as a part of estimating cardiac risk. Low functional status increases the risk of cardiopulmonary complications independent of other risk factors. Patients who require emergent or urgent surgery are at increased risk of a perioperative cardiovascular event.

Postoperative Pulmonary Complications

Postoperative pulmonary complications play a significant role in perioperative morbidity and mortality. There are several pulmonary risk prediction tools including the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk index [5], the Arozullah respiratory failure index [6], and the Gupta calculators for postoperative respiratory failure and pneumonia.

Postoperative pulmonary complications can present in various ways such as atelectasis, bronchospasm, pneumonia, pulmonary edema, pulmonary embolism, aspiration, and postoperative respiratory failure requiring ventilator support. Exacerbation or worsening of preexisting lung conditions such as sleep apnea can

occur as well in the perioperative period. Major causative factors leading to postoperative pulmonary complications are those procedures that result in reduced lung volumes measured by vital capacity and functional residual capacity. This may occur with thoracic and upper abdominal surgery.

Older age, dependent functional status, American Society of Anesthesiologist (ASA) class >2, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and heart failure are patient related pulmonary complication risk factors.

Proximity of the surgical incision to the lung, longer duration of surgery, and emergent surgery are some procedural related risks. General anesthesia carries a higher risk in comparison to regional, epidural, regional anesthesia.

A focused clinical evaluation can identify the patients that are at risk of postoperative pulmonary complications. This can identify unknown pulmonary conditions as well as assess for the status of known conditions. Preoperative test to be considered include pulse oximetry, chest radiographs, pulmonary function, and exercise testing.

Suggested strategies to reduce postoperative pulmonary complications include smoking cessation. This reduces airway reactivity, improves mucociliary function, and decreases carboxyhemoglobin. It has been demonstrated that there is no harm related to a short duration of smoking cessation preoperatively. Other risk factors that can be modified include asthma and COPD control. These conditions may be treated with scheduled inhaled bronchodilator use prior to intubation. Lung expansion maneuvers such as incentive spirometry are also suggested. Empirical continuous positive airway (CPAP) use may be of benefit in certain patients. Measures such as coughing, deep breathing, oral care, head end of bed elevation, and physical therapy may be of benefit. Finally patient and family education on all of these measures has shown to reduce postoperative pulmonary complications [7].

Renal Complications

Acute kidney injury can occur in the postoperative period. Acute kidney injury is defined as a rapid loss of renal function and is associated with significant morbidity and mortality. Various definitions and criteria exist to define acute kidney injury. These are based on the increase in serum creatinine from the baseline over time and the urine output.

Risk factors for perioperative acute kidney injury include the type of surgery. High-risk surgeries include cardiac surgery transplant surgery, abdominal aortic surgery, and emergent surgery [8]. A specific risk is associated with cardiac valve surgery. Patient related risk factors include preexisting chronic kidney disease, diabetes mellitus, congestive heart failure, and peripheral vascular disease. Hypotension in the perioperative period is a significant cause of acute renal failure.

Measures that may reduce the risk of perioperative acute kidney injury include minimally invasive surgical techniques, optimizing the volume status, maintaining

adequate hemodynamic status to ensure renal perfusion, and avoiding nephrotoxin use [9]. This includes minimizing the use of nonsteroidal anti- inflammatory agents (NSAIDS), radio contrast agents, amino glycosides, and in particular the use of amphotericin.

Surgery in Patients with Liver Disease

Patients with chronic liver disease such as cirrhosis who undergo surgery are at increased risk of morbidity and mortality [10]. Risk factors for perioperative morbidity and mortality in patients with cirrhosis include the type of surgery. Increased risk is seen with abdominal and cardiac surgery. Patient risk factors include the presence of ascites, coagulopathy, or encephalopathy. Risk predictors in patients with cirrhosis are Child-Pugh (CP) class, Model for End-stage Liver Disease (MELD). A mortality risk assessment tool developed at the Mayo Clinic is available to calculate the estimated 7-day, 30-day, 90-day, 1-year, and 5-year mortality rates after surgery based on the patient's age, ASA class, and international normalized ratio (INR), serum bilirubin, and serum creatinine [11].

Specific strategies to reduce complications in patients with liver disease undergoing surgery are not widely known. For this reason the decision to proceed with surgery in this population must be done with caution and with an increased emphasis on risk and benefit.

Postoperative Delirium

Postoperative delirium is a common neurological complication. Delirium is an acute reversible confusional state with alteration of consciousness often manifesting as agitation or hallucinations. The condition is often caused by a medical condition, medication, or in combination with the physiological stress of surgery.

The two most important risk factors for postoperative delirium are preexisting dementia and older age. A focused clinical evaluation can unmask preexisting dementia, as well as assess for medical conditions that may predispose the patient to post-op delirium. Medications commonly used in the perioperative period such as opioids, benzodiazepines, and anticholinergics can cause delirium. Their use should be assessed preoperatively [12].

There are challenges in treating postoperative delirium with no single agent or activity providing consistent improvement. A combination of non-pharmacological interventions has been suggested to reduce postoperative delirium. These include orientation, cognitive stimulation, and facilitation of physiologic sleep [13]. Early mobilization and minimized use of physical restraints has been shown to be of benefit. In general those measures that return the patient to a normal cycle of daily activities appear to be beneficial. Many of these measures

are time consuming by staff and should be protocol driven. Currently available evidence does not support the use of pharmacological agents to prevent delirium.

Hematological Complications

Anemia is commonly seen in the perioperative period and transfusion is often undertaken. Transfusion guidelines have been published by various societies. The trend has been towards a more restrictive red blood cell transfusion strategy. The current threshold for transfusion is hemoglobin level of 6–8 g/dL. This should be determined on an individual basis. In general, the different guidelines have recommended that transfusion is not indicated for hemoglobin >10 g/dL [14]. The decision to transfuse should, however, be based on the clinical context rather than any absolute hemoglobin level.

Endocrine System

Stress Dose Steroids

Hypothalamic pituitary adrenal axis can be suppressed with chronic glucocorticoid therapy. During stressful situations such as in the perioperative period, adrenal glands may not respond appropriately suggesting the possible need for stress dose steroid.

Requirements of stress dose steroids should be individualized and based on several factors. This includes the extent of the surgery, dose, and duration of prior steroid treatment and the closeness of the steroid treatment to surgery. In the past, high dose steroids were routinely used for patients who were on any recent steroid treatment. Currently available data suggest that not all patients who are on steroid treatment require stress dose steroids. Stress dose steroids may not be needed unless the steroid use was for primary disease of the hypothalamic pituitary adrenal axis [15]. Additionally the dose of the stress dose steroid is to be based on the extent of the surgery.

Surgery on a Patient with Diabetes Mellitus

Several factors are important to consider in the diabetic patient undergoing surgery. Diabetic patients have a higher incidence of needing surgical procedures than the general population. Coronary artery disease is more common in diabetics than in the

general population. Careful preoperative evaluation is required in this population with reference to the assessment of cardiac status given the likelihood of asymptomatic coronary disease. In addition diabetes mellitus is also associated with increased risk of perioperative infection.

Achieving glycemic control can be difficult in the perioperative period due to various factors affecting the glucose. This includes perioperative nausea, vomiting, and reduced oral intake causing hypoglycemia. Conversely steroid use, infection, stress hormones, and hyperalimentation may cause hyperglycemia. It is preferable that patients with diabetes mellitus should have their surgery earlier in the day. This will allow for adequate resources to manage and stabilize glucose control in the immediate postoperative period.

Preoperative evaluation of a diabetic patient should focus on determination of the type, treatment regimens, adequacy of glucose control, and preexisting complications of diabetes. General anesthesia has greater effects on glucose metabolism and insulin resistance in comparison to epidural or regional anesthesia. Surgery and general anesthesia can cause a neuroendocrine stress response resulting in metabolic abnormalities leading to hyperglycemia.

An elevated hemoglobinA1C level predicts a higher rate of postoperative adverse events. Preoperative or perioperative hyperglycemia in diabetic patients increases the risk of postoperative infection and should be avoided.

Glucose Target in the Perioperative Period

There is no consensus on an ideal glucose in the perioperative period. A lower range of glucose that has been suggested is 80–140 mg/dL. The upper suggested range is 180–200 mg/dL. The target glucose is determined on an individual case based basis taking into account the risk of hypoglycemia. Intensive glucose control (<120–150 mg/dL) was not associated with reduction of infectious complications, mortality, but was associated with hypoglycemia [16].

Insulin for both type one and two is commonly used in the form of sliding scale in the treatment of diabetes in the perioperative period. Basal prandial insulin is preferred over sliding scale alone insulin in the management of type 2 diabetes in a hospital setting [17].

Surgical Wound Related Complications

Risk factors for wound healing issues include peripheral arterial disease, venous insufficiency, prior infection, and radiation. Presence of prosthesis or other foreign body, systemic conditions such as diabetes mellitus, obesity, sickle cell disease, and malnutrition are other well-established factors. The use of immunosuppressant or

chemotherapy may also promote surgical site infections. Additionally requiring blood transfusions and prior tobacco use may be risk factor for both delayed healing and surficial site infection.

Surgical infection prevention measures include use of intravenous prophylactic antibiotic within 1 h before incision, glucose control, and maintaining normothermia [18]. Multiple protocols exist and are mainly determined by the surgical team. Local surgical site observation must be done primarily by the surgical team but the consultant perioperative physician can assist in comorbidity management as well as direct observation of wound sites.

Postoperative Urinary Retention

Postoperative urinary retention is a common problem in the perioperative period and may lead to bladder overdistension, urinary tract infections, unnecessary catheterization, and infections.

Various risk factors have been identified for postoperative urinary retention. Patient specific risk factors are advanced age, men more than women, and the presence of benign prostate hypertrophy. Preexisting neurological conditions such as cerebral palsy and multiple sclerosis also play a factor. Medication used in the perioperative period such as opioids, anticholinergic agents, sympathomimetics may also predispose to urinary retention [19].

Some of the procedure related risk factors are joint arthroplasty, anorectal surgery, hernia repair, and gynecological surgeries.

The overall goal in preventing postoperative urinary retention is to prevent bladder distension, which may further exacerbate the condition while at the same time minimizing catheter use. Depending on preexisting risk factors, patients may require continued use of their benign prostatic hyperplasia (BPH) medications. Careful monitoring of IV fluids and observing for bladder distension during and after surgery is recommended. When necessary, schedule catheterization may be required.

There is no consensus as to what is the best catheterization strategy. However minimizing catheter use driven by protocols is being undertaken at most hospitals. Cholinergic agents, alpha blockers make a significant difference in reducing the incidence of retention.

Perioperative Pharmacology

An important aspect of the preoperative evaluation is to obtain a thorough medication history. This includes nonprescription, over-the-counter medication, supplements, and herbal remedies. Attention should be given to the medication that are used in the intra- and postoperative period and their potential interactions.

Particular emphasis needs to be directed towards the use of anticoagulants and antiplatelet agents. The indications for the use of these medications should be reviewed. Some anticoagulants are held in the perioperative period [20, 21]. Safety of holding medication needs to be determined based on the bleeding risk with the surgery and the medical history. Stent placement, recent thrombotic event, and high-risk atrial fibrillation all pose significant risk when antiplatelet and anticoagulation medicines are stopped. An anticoagulation strategy must be determined for each case and modified when needed.

Medications that are used chronically, if withdrawn abruptly in the perioperative period may be problematic. Certain medicines such as beta-blockers and clonidine have significant hemodynamic affects if stopped and should be continued if possible [22]. Parenteral routes of administration should be considered if the surgery interferes with gastrointestinal function or there are restrictions for oral intake for a prolonged period.

Medication used in the perioperative period can contribute to perioperative complications. Delirium may be seen with opioids, benzodiazepines, anticholinergic medications. If possible their use should be minimized. This should be weighed against the possibility of withdrawal. Renal impairment can be seen with a variety of medicine, including NSAIDs, and their use should be limited.

Prophylactic Beta-Blocker Use in Patients Undergoing Noncardiac Surgery

Perioperative beta-blocker use in patients that are at risk of arterial disease reduces myocardial ischemia, cardiovascular complications. These benefits, however, may be associated with an increase of other risks such as overall mortality and stroke. Randomized controlled trials have yielded conflicting results regarding the ability of beta-blockers to influence perioperative cardiovascular morbidity and mortality in all populations. These variations seem to be based in part on the dose of the beta-blocker and timing of initiation of the beta-blocker [23]. Current evidence suggests to not initiate beta-blocker based solely on risk assessment in the perioperative period. Patients who do not have indications for their long-term beta-blocker use may not benefit from perioperative beat-blocker use [23].

Direct Oral Anticoagulants (DOACs)

Direct factor Xa inhibitors (Rivaroxaban, Apixaban) are used for the treatment and prevention of thromboembolic disease, and stroke prevention in patients with atrial fibrillation. Specific reversible agents have not been available in the event of a major bleed with these drugs. Various agents are being considered. Activated

prothrombin complex concentrate seems to be superior to prothrombin complex concentrate or recombinant activated factor 7 in reversing the anticoagulation effect of Rivaroxaban [24]. A direct thrombin inhibitor, dabigatran, is used for the treatment and prevention of thromboembolic disease, stroke prevention in patients with atrial fibrillation. A specific reversal agent, idarucizumab, has been approved by the FDA for use in patients when reversal of anticoagulation from dabigatran [25].

Opioid Free Total Intravenous Anesthesia

Opioid use is very common in the intra- and postoperative periods for pain control and intraoperative use of opioids may be associated with postoperative hyperalgesia and increased analgesic use. Opioid related side effects, such as postoperative nausea and vomiting (PONV), may delay recovery and discharge [26]. The opioid epidemic has placed greater emphasis on reducing or eliminating opioid use in the perioperative time.

Opioid free total intravenous anesthesia uses sedative-hypnotic anesthetic (typically propofol) combined with an analgesic agent that can reduce postoperative nausea and vomiting. Patients are often given intravenous acetaminophen along with intravenous NASIDS. Gabapentin is also often administered. Nerve blocks may be given for a full 72 h. By the time the block is discontinued pain can be managed by non-opioid methods. Results have been promising with reductions in length of stay and complications seen [26].

Enhanced Recovery After Surgery (ERAS)

ERAS/Fast-track surgery protocols are multimodal evidence based perioperative standardized care protocols that significantly reduce physiological stress and postoperative organ dysfunction. They enhance recovery after surgery and expedite return to baseline health and functional status. Outcomes have improved and length of stay has been reduced [27].

ERAS protocols are applied in various phases of the perioperative care (preoperative, intraoperative, postoperative). Some of the elements of the preoperative care are protocol driven medical optimization, patient education. Timing of the surgery reduces the duration of the NPO status. During the intraoperative period, choosing a minimally invasive approach, and when possible avoidance of nasogastric tubes and intra-abdominal drains. During the postoperative period, a focus on nutrition and early ambulation should be undertaken. There is an emphasis on multimodal non-opioid approaches to control postoperative pain, nausea, and vomiting.

With ERAS protocols, many operations which were performed as inpatient are now done as outpatient/day surgery procedures. The ERAS protocols are being applied to complex surgical procedures and have resulted in improved surgical outcomes. The benefits of fast track protocols were first well established in colorectal surgery patients [28]. Data now supports the role of these protocols in other surgeries as well [28].

Perioperative Surgical Home

Perioperative surgical home (PSH) is a concept where the anesthesiologist plays a key role in the perioperative care (pre-, intra-, postoperative phases). Anesthesiologists take a bigger role that their traditional intraoperative care role serving as a perioperative primary care physician or consultant [29, 30]. Literature, both from the US and internationally suggests positive impacts from PSH initiatives [31].

Carbohydrate Loading

Preoperative carbohydrate loading is a concept of administration of a carbohydrate drink a few hours before surgery [32]. This concept is in contrast to the traditional fasting undertaken after midnight on the day prior to surgery. It is felt that carbohydrate loading may reduce insulin resistance and thereby helping perioperative glucose control. Being in a fed state rather than fasting state reduces catabolism with muscle preservation which may result in reduced complications and a decreased length of stay [33, 34]. Further research is needed to determine in which procedures this concept may be of benefit.

Frailty in Surgical Patients

Frail patients are a subset of medically complex patients. They are often elderly with reduced functional status. They are prone to adverse outcomes with surgical interventions. Awareness and measurement of frailty can improve perioperative risk assessment and care of these patients. Several frailty assessment tools are available. Frailty, independent of medical comorbidities predicts postoperative complications and length of stay in older surgical patients [35].

Research is needed to determine if measures reducing frailty measurements are of any practical benefit in reducing complications in this population. If possible measures to improve functional status should be suggested prior to surgery.

Prehabilitation

Patients with reduced functional status, particularly elderly are prone to have postoperative complications (morbidity, mortality, functional decline). Improvement in preoperative functional status may reduce postoperative morbidity and helps with a faster functional recovery [36]. Prehabilitation is a concept of preparing the surgical patient with various modalities such as exercise and nutrition. The goal is to improve the physical condition of the patient. Prehabilitation have been shown to have a positive impact on the length of hospital stay and readmission rates [37].

Advance Care Planning and Informed Consent

There are inherent risks associated with any surgery, and complications, including death may occur. The preoperative evaluation could be a time to address both the specific advance care issues associated with the surgery and advance care directives in general. High-risk surgery patients often lose decision-making capacity as a result of surgical complications. For these reasons, advance care planning prior to surgery may be beneficial. During the informed consent process, surgical patients are informed about the potential surgical, anesthesia complications. The hospitalist or the medical consultant with the knowledge of the potential medical complications can keep the patient informed of those and also discuss ways to reduce the complications enhancing the informed consent process.

Enhanced informed consent may occur in conjunction with the surgeon and the perioperative team. The surgeon is the primary driver of the informed consent process, but the perioperative team may also provide a different perspective for the patient. Care must be taken in determining roles and reducing conflicting information delivered to the patient.

Conclusion

Hospitalists, with their knowledge of preexisting medical conditions, team based approach and experience of caring for the hospitalized patients are well suited to manage the preoperative clinic and perioperative team.

A collaborative team based approach is needed in the increasingly complex field of perioperative care. This includes the hospitalist, primary care provider, anesthesiologist, subspecialist, and surgeon. The multidisciplinary team should also include the pharmacist, physical therapist, nutritionist, and social worker.

This field continues to develop evolving protocols that require a dedicated physician to review and incorporate into hospital systems. The administration of these protocols requires the interaction of many departments within the hospital. The unique background of the hospitalist may make him or her best suited for this task.

References

1. Edwards AF, Slawski B. Preoperative clinics. Anesthesiol Clin. 2016;34(1):1–15. doi:10.1016/j.anclin.2015.10.002.
2. Vazirani S, Lankarani-Fard A, Liang LJ, Stelzner M, Asch SM. Perioperative processes and outcomes after implementation of a hospitalist-run preoperative clinic. J Hosp Med. 2012;7(9):697–701. doi:10.1002/jhm.1968.
3. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043–9.
4. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, Cohen ME. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217(5):833–42.e1-3. doi:10.1016/j.jamcollsurg.2013.07.385.
5. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, Sabaté S, Mazo V, Briones Z, Sanchis J, ARISCAT Group. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010;113(6):1338–50. doi:10.1097/ALN.0b013e3181fc6e0a.
6. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg. 2000;232(2):242–53.
7. Cassidy MR, Rosenkranz P, McCabe K, Rosen JE, McAneny D. I COUGH: reducing postoperative pulmonary complications with a multidisciplinary patient care program. JAMA Surg. 2013;148(8):740–5. doi:10.1001/jamasurg.2013.358.
8. Grayson AD, Khater M, Jackson M, Fox MA. Valvular heart operation is an independent risk factor for acute renal failure. Ann Thorac Surg. 2003;75(6):1829–35.
9. Cheng D, Martin J, Shennib H, Dunning J, Muneretto C, Schueler S, Von Segesser L, Sergeant P, Turina MJ. Endovascular aortic repair versus open surgical repair for descending thoracic aortic disease a systematic review and meta-analysis of comparative studies. Am Coll Cardiol. 2010;55(10):986–1001. doi:10.1016/j.jacc.2009.11.047.
10. Starczewska MH, Mon W, Shirley P. Anaesthesia in patients with liver disease. Curr Opin Anaesthesiol. 2017; doi:10.1097/ACO.0000000000000470. [Epub ahead of print].
11. Kim SY, Yim HJ, Park SM, Kim JH, Jung SW, Kim JH, Seo YS, Yeon JE, Lee HS, Lee SW, Um SH, Byun KS, Choi JH, Ryu HS. Validation of a Mayo post-operative mortality risk prediction model in Korean cirrhotic patients. Liver Int. 2011;31(2):222–8. doi:10.1111/j.1478-3231.2010.02419.x.
12. Iglseder B, Dovjak P, Benvenuti-Falger U, Böhmdorfer B, Lechliner M, Otto R, Roller RE, Sommeregger U, Gosch M. Drug related delerium in the elderly Wien Med Wochenscher. 2010;160(11–12):281–5.
13. Todd OM, Gelrich L, MacLullich AM, Driessen M, Thomas C, Kreisel SH. Sleep disruption at home as an independent risk factor for postoperative delirium. J Am Geriatr Soc. 2017; doi:10.1111/jgs.14685. [Epub ahead of print].
14. Fusaro MV, Nielsen ND, Nielsen A, Fontaine MJ, Hess JR, Reed RM, DeLisle S, Netzer G. Restrictive versus liberal red blood cell transfusion strategy after hip surgery: a decision model analysis of healthcare costs. Transfusion. 2017;57(2):357–66. doi:10.1111/trf.13936.
15. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. Arch Surg. 2008;143(12):1222–6. doi:10.1001/archsurg.143.12.1222.
16. Buchleitner AM, Martínez-Alonso M, Hernández M, Solà I, Mauricio D. Perioperative glycaemic control for diabetic patients undergoing surgery. Cochrane Database Syst Rev. 2012;9(9):CD007315. doi:10.1002/14651858.CD007315.pub2.
17. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P, Umpierrez D, Newton C, Olson D, Rizzo M. Randomized study of basal-bolus insulin therapy in the inpatient

management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care. 2011;34(2):256–61. doi:10.2337/dc10-1407.
18. Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, Nyquist AC, Saiman L, Yokoe DS, Maragakis LL, Kaye KS. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(6):605–27. doi:10.1086/676022.
19. Baldini G, Bagry H, Aprikian A, Carli F. Postoperative urinary retention: anesthetic and perioperative considerations. Anesthesiology. 2009;110(5):1139–57. doi:10.1097/ALN.0b013e31819f7aea.
20. Smith MS, Muir H, Hall R. Perioperative management of drug therapy, clinical considerations. Drugs. 1996;51(2):238–59.
21. Nagelhout J, Elisha S, Waters E. Should I continue or discontinue that medication? AANA J. 2009;77(1):59–73.
22. Baillard C. Preoperative management of chronic medications [Article in French]. Ann Fr Anesth Reanim. 2005;24(11–12):1360–74.
23. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008;371(9627):1839–47. doi:10.1016/S0140-6736(08)60601-7.
24. Schultz NH, Tran HT, Bjørnsen S, Henriksson CE, Sandset PM, Holme PA, Thromb J. The reversal effect of prothrombin complex concentrate (PCC), activated PCC and recombinant activated factor VII against anticoagulation of Xa inhibitor. Thromb J. 2017;15:6. doi:10.1186/s12959-017-0129-1.
25. Reilly PA, van Ryn J, Grottke O, Glund S, Stangier J. Idarucizumab, a specific reversal agent for dabigatran: mode of action, pharmacokinetics and pharmacodynamics, and safety and efficacy in phase 1 subjects. Am J Emerg Med. 2016;34(11S):26–32. doi:10.1016/j.ajem.2016.09.050.
26. Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, Kadioglu H, Salihoglu Z. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. Braz J Anesthesiol. 2015;65(3):191–9. doi:10.1016/j.bjane.2014.05.001.
27. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248(2):189–98. doi:10.1097/SLA.0b013e31817f2c1a.
28. Kehlet H. Multimodal approach to postoperative recovery. Curr Opin Crit Care. 2009;15(4):355–8. doi:10.1097/MCC.0b013e32832fbbe7.
29. Vetter TR, Goeddel LA, Boudreaux AM, Hunt TR, Jones KA, Pittet J-F. The Perioperative Surgical Home: how can it make the case so everyone wins? BMC Anesthesiol. 2013;13:6. doi:10.1186/1471-2253-13-6.
30. Desebbe O, Lanz T, Kain Z, Cannesson M. The perioperative surgical home: an innovative, patient-centred and cost-effective perioperative care model. Anaesth Crit Care Pain Med. 2016;35(1):59–66. doi:10.1016/j.accpm.2015.08.001.
31. Kash BA, Zhang Y, Cline KM, Menser T, Miller TR. The perioperative surgical home (PSH): a comprehensive review of US and non-US studies shows predominantly positive quality and cost outcomes. Milbank Q. 2014;92(4):796–821. doi:10.1111/1468-0009.12093.
32. Burch J. Preoperative carbohydrate loading in the enhanced recovery pathway. Br J Nurs. 2016;25(12):669–72. doi:10.12968/bjon.2016.25.12.669.
33. Pogatschnik C, Steiger E. Review of preoperative carbohydrate loading. Nutr Clin Pract. 2015;30(5):660–4. doi:10.1177/0884533615594013.
34. Nygren J, Thorell A, Ljungqvist O. Preoperative oral carbohydrate nutrition: an update. Curr Opin Clin Nutr Metab Care. 2001;4(4):255–9.
35. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, Takenaga R, Devgan L, Holzmueller CG, Tian J, Fried LP. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210(6):901–8. doi:10.1016/j.jamcollsurg.2010.01.028.

36. Debes C, Aissou M, Beaussier M. Prehabilitation. Preparing patients for surgery to improve functional recovery and reduce postoperative morbidity [Article in French]. Ann Fr Anesth Reanim. 2014;33(1):33–40. doi:10.1016/j.annfar.2013.12.012.
37. Santa Mina D, Scheede-Bergdahl C, Gillis C, Carli F. Optimization of surgical outcomes with prehabilitation. Appl Physiol Nutr Metab. 2015;40(9):966–9. doi:10.1139/apnm-2015-0084.

Chapter 12
Obstetrics: The Hospitalist's Approach to the Pregnant Patient

Veronica Gillispie and Brittany McKinley

Bleeding in the First Trimester

Case Presentation

A 23-year-old Gravida 1 Para 0 female presents to the Emergency Room with complaint of vaginal bleeding. She reports a positive pregnancy test at home. She is unsure of her last menstrual period. She reports the pain is "menstrual-like cramping." She has no medical history and no surgeries in the past. On physical exam, vital signs are stable and she is afebrile. On speculum exam, the cervix appears to be closed with slight vaginal bleeding. On bimanual exam, the uterus feels gravid and the cervix is closed. There is no adnexal tenderness. What is the next step in her management?

Bleeding Secondary to Implantation

Vaginal bleeding during the first trimester of pregnancy can occur for a number of reasons (see Table 12.1). Bleeding may be physiological due to changes in progesterone as the placenta is established [1]. If all other plausible causes of the bleeding are ruled out, then reassurance and follow-up with a normal obstetrics appointment schedule is recommended.

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Table 12.1 Causes of bleeding in the first trimester

Abortion
Complete
Incomplete
Inevitable
Threatened
Ectopic pregnancy
Infection
Physiologic
Implantation
Abrasions of the cervix

Bleeding Secondary to Abortion

Spontaneous abortion is a common cause of first trimester bleeding. Up to 20% of pregnancies will result in spontaneous abortion, and of these, 80% will occur within the first trimester [2, 3]. There are several types of spontaneous abortions: threatened, inevitable, complete, and incomplete are types associated with vaginal bleeding.

A diagnosis of threatened abortion is made when an intrauterine pregnancy at 20 weeks gestation or less is associated with vaginal bleeding. On physical exam, the cervix is closed, there has been no passage of products of conception and on ultrasound, fetal cardiac activity is present. This is the most common type of abortion. Up to 96% of threatened abortions with subsequent confirmed fetal cardiac activity do not result in miscarriage [4, 5]. Expectant management is appropriate in these cases.

Similar to a threatened abortion, an inevitable abortion is a pregnancy at 20 weeks gestation or less that is associated with vaginal bleeding. The key distinction is that inevitable abortion is also associated with cervical dilation. These pregnancies will eventually result in a complete abortion. There are three management options in this type of abortion: expectant, medical, or surgical. Patients that are hemodynamically stable with no signs of infection may be offered expectant or medical management. Patients managed expectantly are given precautions to present to the hospital if they experience heavy vaginal bleeding or severe abdominal pain. They are also instructed to follow up in 1 week after diagnosis to determine if products of conception have passed spontaneously. Medical management includes the use of misoprostol alone or with the addition of mifepristone. The recommended initial dose of misoprostol is 800 μg vaginally. A repeat dose may be administered if needed. This must be administered within 7 days of the initial dose, and no earlier than 3 hours after the first dose [6]. Serial beta-hCG analysis or transvaginal ultrasound is again indicated to ensure that all products of conception have been successfully passed. For patients that are not hemodynamically stable, show signs of infection or decline expectant or medical management, may be treated surgically via a dilation and suction to remove the products of conception [7, 8].

An incomplete abortion is diagnosed when some products of conception have passed but there are still some retained products. This can be determined by ultrasound. Again, if the patient is hemodynamically stable with no signs of infection,

they may be a candidate for expectant or medical management. If they are not candidates or decline conservative management, they should be treated surgically with a dilation and curettage.

A missed abortion is a pregnancy before 20 weeks with no fetal cardiac activity. Patients are asymptomatic (i.e., no vaginal bleeding or abdominal pain). It is generally found on routine exam. These patients can be managed expectantly, medically, or surgically.

A complete abortion is diagnosed when all products of conception have passed, and the cervical os is closed. This is a clinical diagnosis that may be confirmed with serial beta-hCG analysis and transvaginal ultrasound.

Bleeding Secondary to Ectopic Pregnancy

Ectopic pregnancy is another common cause of first trimester bleeding. Ectopic pregnancy occurs when an embryo has implanted in a site outside the uterus. The most common site of extrauterine pregnancy is the ampulla of the fallopian tube [9]. As the embryo grows, it can cause expansion or rupture of the fallopian tube, resulting in vaginal or intra-abdominal bleeding. Any patient with a confirmed pregnancy that presents with vaginal bleeding should be evaluated for the location of pregnancy (i.e., extrauterine vs. intrauterine) as ruptured ectopic pregnancy is a surgical emergency. Patients with a ruptured ectopic pregnancy may present with diffuse abdominal pain or peritoneal signs.

Ectopic pregnancy can be diagnosed with a beta-hCG level that is greater than 2000 IU/L in the setting of a transvaginal ultrasound that shows an absent intrauterine pregnancy [10]. A non-ruptured ectopic pregnancy can be managed medically or surgically. Methotrexate is the gold standard for medical management. Absolute contraindications include hemodynamically instability, active liver disease, and unreliable patient. Relative contraindications include a beta-hCG of >5000 IU/L, gestational sac >3.5 cm, or the presence of fetal cardiac activity [11]. Surgical intervention is recommended when the criteria for medical management are not met. The surgical approach can be laparoscopic or via a laparotomy. The surgical approach should be determined based on the experience of the surgeon with each skill as well as the stability of the patient. Once the approach is determined, surgical treatment can be a salpingectomy or salpingostomy. Salpingostomy may be preferred for women who desire to maintain fertility. However, the risk of ectopic pregnancy in future pregnancies is increased [12]. Salpingectomy is necessary when the fallopian tube is ruptured.

Bleeding Secondary to Infection

Infection is another cause of first trimester bleeding. Infections can cause vaginal or cervical irritability, resulting in spotting during the first trimester of pregnancy. Some common infectious agents include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Gardnerella vaginalis*, and *Candida albicans*. Chlamydia is the most common

Table 12.2 Amsel criteria for the diagnosis of bacterial vaginosis

Discharge that is thin and gray, white, or yellow
Fishy odor in the presence of 10% KOH
Vaginal pH that is >4.5
Clue cells on microscopy

sexually transmitted infection, while gonorrhea is the second most common infection [13]. To diagnose an infection, a first-catch urine sample or a vaginal swab must be obtained for testing. A nucleic acid amplification test (NAAT), which is the gold standard for diagnosis, is then used for detection [14]. The CDC currently recommends one dose of oral azithromycin 1 g as a single dose. For women who cannot tolerate this, erythromycin or amoxicillin can be used [15]. A single injection of ceftriaxone 250 mg plus azithromycin 1 g orally in a single dose is the treatment for gonococcal infections. If ceftriaxone is not available, Cefixime 400 mg orally in a single dose plus azithromycin is recommended [16]. Gardnerella is a common cause of bacterial vaginosis and is another source of first trimester vaginal bleeding. Diagnosis can be made using the Amsel criteria which includes presence of a thin gray–white vaginal discharge, fishy odor in the presence of 10% KOH, a pH > 4.5, and presence of clue cells on microscopy (see Table 12.2) [17]. It is important to note that while a Gram stain is the gold standard for diagnosis, it is not commonly used in clinical practice [18]. Treatment for Gardnerella should be deferred until the second trimester. Clindamycin 300 mg bid for 7 days, metronidazole 500 mg bid for 7 days, or metronidazole 250 mg tid for 7 days can be used for treatment [19]. Candida is another common cause of a vaginosis. Patients may be asymptomatic, or present with thick white discharge with burning, itching, dysuria, dyspareunia, and bleeding [20]. Diagnosis is clinical and can be confirmed with a wet mount to visualize sampled discharge. 10% KOH can be used to better visualize the characteristic budding and pseudohyphae of the yeast [21]. Treatment is only recommended for symptomatic patients, as infection is not associated with adverse pregnancy outcomes [22]. Clotrimazole or miconazole can be used in combination with topical cream for symptomatic cases [23]. Oral fluconazole should be avoided, as there is some evidence that it may be associated with increased risk of spontaneous abortions [18].

Case Conclusion

In conclusion, vaginal bleeding in the first trimester can be due to a number of reasons. In this case, a woman who is hemodynamically stable presents with vaginal bleeding in the setting of a positive home pregnancy test. The positive home pregnancy test must first be confirmed with a urine pregnancy test. Once pregnancy is confirmed, a physical exam can be safely conducted. In this case, the speculum exam reveals a closed cervix and blood within the vaginal vault. An ultrasound would then be warranted to confirm intrauterine pregnancy. In this case, an intrauterine pregnancy is visualized, and fetal heart tones are heard, so ectopic pregnancy is ruled out.

In the absence of a vaginal or cervical infection, we can diagnose this as a threatened abortion. A complete blood count and type and screen should also be ordered at this time. If the mother is Rhesus factor (Rh) negative and the patient has experienced bleeding, Anti-D or Rhogam should be administered [24]. A 50 μg dose of Rhogam can be administered for all first trimester pregnancies, though it is safe to use the standard dose of 300 μg if that is more readily available [25]. In this patient, it is appropriate to manage her expectantly giving her precautions to return to the emergency room if her bleeding increases or her pain becomes more severe.

Nausea and Vomiting

Introduction

Nausea and vomiting, or "morning sickness," is a common complaint in pregnancy, and affects up to 74% of pregnant patients [26]. Typically, nausea and vomiting begins around weeks five and six, peaks at week nine, and improve after week 16 [27]. This is attributed to rising first trimester beta-hCG levels, which double every 48–72 h from conception until weeks 9–12 before declining. However, the true pathogenesis of nausea during pregnancy remains unknown, with some known causes including pregnancy-related complications, gastrointestinal conditions, endocrine disorders, and infection (see Table 12.3).

Pregnancy-Related Causes

Some common pregnancy-related etiologies include hyperemesis gravidarum, acute fatty liver disease of pregnancy, and HELLP syndrome.

Hyperemesis gravidarum is a serious condition. It presents in the first couple weeks of pregnancy, and is defined as severe nausea and vomiting resulting in

Table 12.3 Causes of nausea and vomiting in pregnancy

Pregnancy-related complications
Hyperemesis gravidarum
Acute fatty liver disease of pregnancy
Pre-eclampsia
HELLP syndrome
Gastrointestinal conditions
Appendicitis
Cholecystitis
Endocrine disorders
Diabetic ketoacidosis
Hyperthyroidism
Infection
Pyelonephritis

dehydration and a loss of 5% of pre-pregnancy weight. Hyperemesis gravidarum can occur in normal pregnancies, but can also be a sign of a serious underlying condition, such as a trophoblastic disease [28]. The diagnosis of hyperemesis gravidarum is clinical, but can be supported by metabolic changes seen on blood work. Blood work includes a complete metabolic panel, which typically shows a hypochloremic metabolic alkalosis, caused by the electrolyte imbalance from the persistent vomiting. Increased liver enzymes (less than 300 units/L), increased serum bilirubin (less than 4 mg/dL), and increased serum amylase (up to five times greater than normal levels) may also be present [29].

Acute fatty liver disease is a rare condition, affecting 5 in 100,000 pregnancies. Women with low BMI (<20) or multiple gestations are shown to be at greater risk [30]. Acute fatty liver disease typically presents in the third trimester with nausea and vomiting as the primary symptom. Other symptoms include epigastric abdominal pain, anorexia, jaundice, and malaise [31]. Laboratory tests will show elevated serum aminotransferase (up to 500 units/L). Severe cases may also have elevated serum ammonia and prolonged prothrombin time, as well as hypoglycemia. Acute kidney injury and hyperuricemia are also often present [32]. Imaging tests of the liver are primarily used to exclude other diagnoses, while liver biopsy is used for definitive diagnosis [33]. Liver biopsy will show fatty change, or more specifically, microvesicular fatty infiltration of the hepatocytes [34].

It is also important to consider HELLP syndrome, or **H**emolysis, **E**levated **L**iver enzymes, and **L**ow **P**latelets syndrome in this setting, as there are many overlapping features between this and acute fatty liver disease of pregnancy. HELLP syndrome can also present with nausea and vomiting in the third trimester, although the most common symptom is abdominal pain and tenderness [35]. Findings may include hypertension (blood pressure ≥140/90 mmHg) and proteinuria, which are present in 85% of cases [36]. Diagnosis is made when the Tennessee Classification Criteria are met, which includes a blood smear showing evidence of microangiopathic hemolytic anemia, platelet count of ≤100,000 cells/μL, total bilirubin ≥1.2 mg/dL, and serum AST >2 (see Table 12.4) [35]. HELLP is closely related to pre-eclampsia, another complication found in pregnancy.

Pre-eclampsia is a common complication, affecting approximately 4.6% of pregnancies worldwide [37]. It is a serious condition that can progress to eclampsia (pre-eclampsia with seizures) or HELLP syndrome (previously discussed). It is responsible for 10–15% of direct maternal deaths [38]. Pre-eclampsia can present with nausea and vomiting in the setting of epigastric pain, although the most common presentation is that of headache. Visual changes, hyperreflexia, and pulmonary or general edema may also be present. Diagnosis requires evidence of new onset severe hypertension (≥140/≥90), with either proteinuria (≥1+ on urine dipstick,

Table 12.4 Tennessee classification criteria for the diagnosis of HELLP syndrome

Blood smear showing microangiopathic hemolytic anemia
Platelet count ≤100,000 cells/μL
Total bilirubin ≥1.2 mg/dL
Serum AST >2

protein:creatinine ratio >0.3 mg, ≥0.3 g protein in a 24-h urine specimen), or evidence of end organ dysfunction in a patient who is ≥20 weeks gestation [39].

Gastrointestinal Causes

Several gastrointestinal conditions also cause nausea and vomiting in both pregnant and non-pregnant patients. The gastrointestinal conditions considered here are appendicitis and cholecystitis.

Acute appendicitis is suspected in 1/600–1/1000 pregnancies and confirmed in 1/800–1/1500 pregnancies [40–43]. The classic presentation of appendicitis includes right upper quadrant or periumbilical pain that migrates to the right lower quadrant, followed by nausea and vomiting, anorexia, fever, and leukocytosis [44]. However, pregnant patients are less likely to present with these classical features, and are more likely to present with non-classical features such as heartburn, constipation or diarrhea, flatulence, and malaise [45]. It is important to note that the appendix will be more anteriorly located as pregnancy progresses. Diagnosis is histological, but imaging modalities should also be used in diagnosis, in order to prevent removal of histologically normal appendices. Ultrasound is the best initial imaging modality for all pregnant patients. If the ultrasound is inconclusive, MRI can be used [46–48].

Cholecystitis has a number of etiologies. Gallstones are more common in pregnant patients than non-pregnant patients, though it remains an uncommon cause overall [49]. Cholecystitis presents as severe right upper quadrant or epigastric pain that can radiate to the right shoulder or back. The pain is typically worsened by fatty food ingestion. Fever, nausea and vomiting, and anorexia can also be present. Leukocytosis will be seen on a complete blood count. Elevation of the serum total bilirubin and alkaline phosphatase concentrations are not present in acute cholecystitis, but may be elevated in conditions such as cholangitis or choledocolithiasis, and can therefore be used to differentiate between these different conditions [50].

Physical exam will reveal severe pain to deep palpation of the right upper quadrant, also known as Murphy's sign [50]. Diagnosis is either with abdominal ultrasound, which demonstrates gallbladder wall thickening or edema, or cholescintigraphy, which shows abnormal filling of the gallbladder [51].

Endocrine Causes

Endocrinopathies including diabetic ketoacidosis (DKA), and hyperthyroidism must also be considered in a patient with nausea and vomiting. DKA is a medical emergency that should not be missed. DKA can present with nausea and vomiting, as well as abdominal pain [52]. Diagnostic evaluation includes laboratory tests which confirm hyperglycemia, anion gap metabolic acidosis, and ketonemia. Serum glucose levels may be greater than 350 mg/dL [53, 54]. Presence of ketonemia is first determined by

analyzing for the presence of ketone bodies in the urine using a nitroprusside test [55]. If positive, a serum beta-hydroxybutyrate should be ordered to confirm ketonemia [56].

Hyperthyroidism is a serious condition in pregnancy that can cause hyperemesis gravidarum, as well as a number of pregnancy-related complications, including increased risk of pre-eclampsia, heart failure, and fetal adverse effects [57, 58]. Though it is relatively uncommon, occurring in 0.1–0.4% of all pregnancies, it is an important condition to consider [59, 60]. Though there are many etiologies, Graves' disease is the most common cause of hyperthyroidism, accounting for 95% of these cases [61]. Symptoms of hyperthyroidism includes nausea and vomiting, weight loss despite a normal or increased appetite, tachycardia, palpitations, heat intolerance, increased perspiration, and fine hand tremor. Diagnosis requires a TSH level, followed by a free T3 and T4 level. Overt hyperthyroidism will show a low TSH level and high free T4 level [62, 63].

Infectious Causes

Infection is another important cause of nausea and vomiting in pregnancy. An important source of infection to consider is a urinary tract infection. Asymptomatic urinary tract infections affect 2–7% of all pregnant women [64, 65]. 0.5–2% of these cases progress to pyelonephritis [66–69]. This most commonly occurs in the second and third trimesters of pregnancy [70]. Pyelonephritis presents as nausea and vomiting, flank pain or costovertebral angle tenderness, and fever. Symptoms of cystitis, such as dysuria, urgency, and frequency, may also be present, though pyuria is a common finding [71, 72].

Diagnosis is made with a urinalysis and urine culture with susceptibility testing. Urinalysis and culture should show bacteria, as well as pyuria. It is recommended that patients with pyelonephritis be admitted for IV antibiotics. Broad spectrum beta-lactams is the treatment of choice for pregnant patients, though IV ampicillin 1–2 g IV q6h and gentamicin IV 1.5 mg/kg q8h can also be used [73]. IV antibiotics are typically administered for 24–48 h, or until the patient is afebrile for more than 24 h. The patient can then be discharged on a 10- to 14-day course of oral antibiotics appropriate for the cultured organism. Patients should also receive a prophylactic dose of antibiotics throughout the pregnancy to prevent reoccurance [74].

Non-pharmacological Management

Nausea and vomiting can be managed with non-pharmacological and pharmacological means (Table 12.5). Non-pharmacological treatments include dietary modification, herbs and vitamins, and acupuncture. Dietary modifications include limiting the diet to carbohydrate or protein rich snacks and avoiding foods that are inherently tough to digest, including spicy, acidic, high-fat, or overly odorous foods [75, 76]. Pregnant

Table 12.5 Treatment of nausea and vomiting in pregnancy

Non-pharmacological
Dietary modifications
Herbs
Vitamins
Acupuncture
Pharmacological
Antihistamines
Doxylamine 10 mg + pyridoxine 10 mg HS
Diphenhydramine 25–50 mg Q4-6H
Dimenhydrinate 25–50 mg Q4-6H
Meclizine 25 mg Q4-6H
Dopamine antagonists
Metoclopramide 10 mg IM or IV Q6-8H
Promethazine 12.5–25 mg PO, IM, or PR Q4H
Serotonin antagonists
Ondansetron 4 mg PO or IV Q8H
Glucocorticoids
Methylprednisolone 16 mg IV Q8H
Hydrocortisone 100 mg IV BID

women should eat small, frequent meals and avoid hunger which may elicit feelings of nausea [77]. It is known that peppermint may aid in postprandial nausea [78].

Cold, clear carbonated drinks are generally tolerated better than other liquids, and should be chosen over drinks that are hard on the digestive system, such as coffee [27]. Herbs, such as ginger, have also proved beneficial in alleviating nausea. There are many ginger-containing products, such as ginger tea, lollipops, foods, and sodas, but it can also be prescribed in a powdered form to be added to foods. Recommended dosing is 1–1.5 g/24 h [79].

Acupuncture is another non-pharmacological modality that has been explored in alleviating nausea and vomiting, but unfortunately, has shown conflicting [80].

Pharmacological Management

Pyridoxine, or vitamin B6, has also been shown to be effective in treating nausea [27]. Pyridoxine 10–25 mg can be taken every six to 8 h, and should not exceed 200 mg/day. It is important to note that doses exceeding 500 mg/day may have unknown effects on the fetus and can cause peripheral neuropathy in the mother [81, 82]. If a trail of pyridoxine fails, doxylamine succinate, an over-the-counter antihistamine, can be added to the regimen. The recommended dosing is 10 mg pyridoxine combined with 10 mg doxylamine at bedtime [83, 84].

Pharmacological treatment includes antihistamines, dopamine antagonists, and serotonin antagonists. Antihistamines are considered first-line treatment for nausea and vomiting in pregnancy, and includes doxylamine with pyridoxine as previously discussed, diphenhydramine and dimenhydrinate, and meclizine.

Diphenhydramine and dimenhydrinate are antihistamines that block H1-receptors and associated nausea and vomiting. They are prescribed at a starting dose of 25–50 mg every 4–6 h as needed [85–87]. Meclizine 25 mg can be used if diphenhydramine and dimenhydrinate therapy fails. It is important to note that some animal studies have shown an increased rate of cleft palate malformations with the use of meclizine [88–90].

Dopamine antagonists are considered second-line in the treatment of nausea and vomiting in pregnancy and include metoclopramide and promethazine. Metoclopramide 10 mg can be given IM or IV every 6–8 h [91]. Adverse effects include movement disorders such as dystonia, tardive dyskinesia, and parkinsonism, which can be permanent or resolve with discontinuation of the drug [92]. Promethazine has effects on both histamine and dopamine receptors. Promethazine 12.5–25 mg can be given PO, IM, or PR, every 4 h as needed. It has similar adverse effects to that of metoclopramide [93].

Serotonin antagonists such as ondansetron are considered for refractory cases of nausea and vomiting in pregnancy, and are also useful for the treatment of hyperemesis gravidarum. It is considered a third-line treatment due to its limited safety and efficacy profile. The starting dose is 4 mg PO or IV every 8 h as needed. Adverse effects are numerous and include headache, fatigue, drowsiness, constipation, and in rare cases, QTc prolongation and serotonin syndrome [94, 95].

Refractory Cases

Severe or refractory cases of nausea and vomiting can be treated with glucocorticoids. An effective regimen includes methylprednisolone 16 mg given IV every 8 h for 48–72 h [96]. An alternative regimen includes hydrocortisone 100 mg IV twice daily [97]. Glucocorticoids are associated with an increased risk of fetal cleft lip when administered before the tenth week of pregnancy, and should therefore be avoided in the first trimester of pregnancy [98–102].

Conclusion

The pathophysiology of nausea and vomiting is not well understood. Some conditions that present with nausea and vomiting includes hyperemesis gravidarum, acute fatty liver disease of pregnancy, pre-eclampsia, HELLP syndrome, appendicitis, cholecystitis, DKA, hyperthyroidism, and pyelonephritis. Other conditions include, but are not limited to, gastroparesis, ovarian torsion, nephrolithiasis, migraines, and drug allergies [27]. Treatment is the same regardless of the underlying condition.

Select Review of Medical Conditions in the Pregnant Patient

Introduction

Pregnant patients may present to the hospital with new or underlying medical conditions. It is important to get a comprehensive medical history, as some of these conditions may complicate the pregnancy. Medical conditions that are managed pharmacologically may require different medications than as in non-pregnant patients, as many drugs are teratogenic. Asthma and heart failure are two of many medical conditions that will be discussed in this section.

Asthma: Summary of Recommendations

Asthma is one of the most common medical conditions encountered in pregnant patients, occurring in 3–8% of patients [103]. Poorly controlled asthma may result in complications such as pre-term delivery or low birth weight [104, 105]. Patients with a previous diagnosis of asthma may experience a worsening of asthma symptoms in pregnancy [106]. Fortunately, asthma management in pregnant patients is similar to those of non-pregnancy patients.

It is important to note that there are some minor differences that will be discussed here. For relief of acute asthma symptoms, albuterol, a short-acting beta-agonist, is preferred over other medications (see Table 12.6). For patients requiring the use of the albuterol inhaler more than twice a week, budesonide, an inhaled glucocorticoid, is preferred over long-acting beta-agonists and other steroid treatments [108–110]. Some studies have shown that use of systemic glucocorticoids may result in increased risk of low birth weight, cleft palate malformation, and congenital adrenal insufficiency [111–114]. For acute exacerbations requiring hospital admission, terbutaline administration is preferred over epinephrine administration. This is because epinephrine causes vasoconstriction of the uterine artery, and therefore decreased blood supply to the placenta and fetus [115–117]. Monotherapy is generally preferred over dual therapy.

Heart Failure: Summary of Recommendations

Heart failure is another medical condition that can complicate pregnancy. When a patient presents with signs and symptoms of acute heart failure, it is important to consider both new onset heart failure and acute on chronic heart failure. Fortunately, the diagnosis and treatment of heart failure in pregnant patients is

Table 12.6 Management of acute asthma exacerbation in pregnancy [107]

First line:
Albuterol
MDI: 4–8 puffs Q20 min for 1 h, then every 1–4 h prn, or
Nebulizer: 2.5–5 mg Q20 min × 3, then every 1–4 h prn, or
Continuous nebulizer: 10–15 mg/h
Adjuvant therapy:
Ipratropium
MDI: 4–8 inhalations Q20 min × 3, then prn
Nebulizer: 500 mcg Q20 min × 3
Failure to progress at 1H, add:
Prednisone
40–80 mg/day, or
Methylprednisolone
60–80 mg IV or PO Q6-8H, followed by taper
Refractory cases:
$MgSO_4$ 2 g IV over 20 min
Terbutaline 0.25 mg IM Q20 min × 3

similar to that of non-pregnant patients. However, it is important to recognize that certain pharmacological drugs are preferred in pregnancy, while others should be avoided [118].

Angiotensin Converting Enzyme inhibitors (ACE-i) and Angiotensin II Receptor Blockers (ARBs) should be avoided due to their teratogenic effects of the fetus. They should be stopped immediately if pregnant, and not started again until the patient is no longer breastfeeding [119–121]. A trial of hydralazine and isosorbide dinitrate can be tried in place of an ACE-i or ARB [117, 122]. If a beta-blocker need to be initiated, metoprolol is the drug of choice due to its low excretions in the breastmilk compared to other beta-blockers [123, 124]. Loop diuretics are the diuretics of choice in pregnancy, and are preferred over thiazides and potassium-sparing diuretics. If a loop diuretic is not sufficient, an addition of a thiazide may be considered. It is important to note that thiazides have been associated with increased risk of hyponatremia and bleeding diathesis in neonates [125]. Aldosterone antagonists, such as spironolactone, should not be used in pregnancy due to its adverse effects of the fetus [126].

In the management of acute exacerbation of CHF in which venous thromboembolism prophylaxis needs to be started, heparin is recommended. Low molecular weight heparin (LMWH) is generally preferred, but unfractionated heparin can also be used, especially when there is renal impairment [127–129]. The specific treatment regimen for heart failure depends on the type of heart failure. The types of heart failure considered here include acute decompensated heart failure, heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). The appropriate treatment regimen for each is outlined in Table 12.7.

Table 12.7 Treatment of heart failure in pregnancy

Acute decompensated heart failure
O_2
Digoxin
Diuretic
VTE prophylaxis
HFrEF
Diuretic
Beta-blocker
Hydralazine + Isosorbide Dinitrate
± digoxin for severe or refractory cases
HFpEF
Diuretic
Beta-blocker
Hydralazine + Isosorbide Dinitrate

Conclusion

Many underlying medical condition can worsen in pregnancy, or arise de novo. Fortunately, many of these conditions can be managed as in non-pregnant patients. The important factor to consider when managing a pregnant patient is the potential adverse effects a drug may have on the fetus. Before administering any pharmaceutical agent, make sure to first consult the safety and efficacy of the product.

Key Points

- Pregnant patients who present to hospital may not necessarily warrant an Obstetrics and Gynecology consult.
- Bleeding in the first trimester is not always pathologic, and can be due to normal implantation.
- The pathophysiology of nausea and vomiting is not well understood, but there are a number of medical conditions that present with it, as well as number of pharmacological and non-pharmacological means to treat it.
- Medical conditions can either arise de novo or be worsened in pregnancy due to the normal physiologic changes the body undergoes when pregnant.
- One of the most important considerations when treating a medical condition in a pregnant patient is to identify any potential adverse effects a drug may have on the fetus.

References

1. Bleeding during pregnancy. The American College of Obstetrician and Gynecologists. FAQ038; July 2016.
2. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. N Engl J Med. 1988;319(4):189–94.
3. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril. 2003;79(3):577–84.
4. Tongsong T, Srisomboon J, Wanapirak C, Sirichotiyakul S, Pongsatha S, Polsrisuthikul T. Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study. J Obstet Gynaecol (Tokyo 1995). 1995;21(4):331.
5. Tannirandorn Y, Sangsawang S, Manotaya S, Uerpairojkit B, Samritpradit P, Charoenvidhya D. Fetal loss in threatened abortion after embryonic/fetal heart activity. Int J Gynaecol Obstet. 2003;81(3):263.
6. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM, National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med. 2005;353:761–9.
7. Tunçalp Ö, Gülmezoglu AM, Souza JP. Surgical procedures for evacuating incomplete miscarriage. Cochrane Database Syst Rev. 2010;(9):CD001993. doi: 10.1002/14651858.CD001993.pub2.
8. Rogo K. Improving technologies to reduce abortion-related morbidity and mortality. Int J Gynaecol Obstet. 2004;85(Suppl 1):S73–82.
9. Bouyer J, Coste J, Fernandez H, Pouly JL, Job-Spira N. Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. Hum Reprod. 2002;17(12):3224.
10. van Mello NM, Mol F, Ankum WM, Mol BW, van der Veen F, Hajenius PJ. Ectopic pregnancy: how the diagnostic and therapeutic management has changed. Fertil Steril. 2012;98(5):1066–73.
11. Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med. 1999;341(26):1974.
12. Mol F, van Mello NM, Strandell A, Strandell K, Jurkovic D, Ross J, Barnhart KT, Yalcinkaya TM, Verhoeve HR, Graziosi GC, Koks CA, Klinte I, Hogström L, Janssen IC, Kragt H, Hoek A, Trimbos-Kemper TC, Broekmans FJ, Willemsen WN, Ankum WM, Mol BW, van Wely M, van der Veen F, Hajenius PJ, European Surgery in Ectopic Pregnancy (ESEP) Study Group. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): an open-label, multicentre, randomised controlled trial. Lancet. 2014;383(9927):1483–9.
13. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance, 2015. Atlanta, GA: US Department of Health and Human Services; 2016.
14. Centers for Disease Control and Prevention. Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae—2014. MMWR Recomm Rep. 2014;63(RR-02):1.
15. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep. 2015;64(RR-03):1–137.
16. Sexually transmitted diseases treatment guidelines. Atlanta, GA: US Department of Health and Human Services; 2016.
17. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. Clin Infect Dis. 2007;44(Suppl 3):S84–101.
18. Cotch MF, Hillier SL, Gibbs RS, Eschenbach DA. Epidemiology and outcomes associated with moderate to heavy Candida colonization during pregnancy. Vaginal Infections and Prematurity Study Group. Am J Obstet Gynecol. 1998;178(2):374.
19. Spiegel CA. Bacterial vaginosis. Clin Microbiol Rev. 1991;4(4):485.

20. Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. Obstet Gynecol. 1998;92(5):757–65.
21. National guideline for the management of vulvovaginal candidiasis. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). Sex Transm Infect. 1999;75(Suppl 1):S19.
22. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74(1):14.
23. Rex JH, Walsh TJ, Sobel JD, Filler SG, Pappas PG, Dismukes WE, Edwards JE. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. Clin Infect Dis. 2000;30(4):662.
24. Von Stein GA, Munsick RA, Stiver K, Ryder K. Fetomaternal hemorrhage in threatened abortion. Obstet Gynecol. 1992;79(3):383–6.
25. Wylie BJ, D'Alton ME. Fetomaternal hemorrhage. Obstet Gynecol. 2010;115(5):1039.
26. Herrell HE. Nausea and vomiting of pregnancy. Am Fam Physician. 2014;89(12):965–70.
27. Association of Professors of Gynecology and Obstetrics. Nausea and vomiting of pregnancy. https://www.apgo.org/. Accessed 05 Dec 2016.
28. Soto-Wright V, Bernstein M, Goldstein DP, Berkowitz RS. The changing clinical presentation of complete molar pregnancy. Obstet Gynecol. 1995;86(5):775.
29. Niemeijer MN, Grooten IJ, Vos N, Bais JM, van der Post JA, Mol BW, et al. Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;211:150.e1–15.
30. Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P, UK Obstetric Surveillance System. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57(7):951.
31. Riely CA. Acute fatty liver of pregnancy. Semin Liver Dis. 1987;7(1):47.
32. Grünfeld JP, Pertuiset N. Acute renal failure in pregnancy: 1987. Am J Kidney Dis. 1987;9(4):359.
33. Barton JR, Sibai BM. Hepatic imaging in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Am J Obstet Gynecol. 1996;174(6):1820.
34. Bacq Y. Acute fatty liver of pregnancy. Semin Perinatol. 1998;22(2):134.
35. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol. 1993;169(4):1000.
36. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol. 2004;103(5 Pt 1):981.
37. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1–7.
38. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130–7.
39. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122.
40. Andersen B, Nielsen TF. Appendicitis in pregnancy: diagnosis, management and complications. Acta Obstet Gynecol Scand. 1999;78(9):758.
41. Mourad J, Elliott JP, Erickson L, Lisboa L. Appendicitis in pregnancy: new information that contradicts long-held clinical beliefs. Am J Obstet Gynecol. 2000;182(5):1027.
42. Mazze RI, Källén B. Appendectomy during pregnancy: a Swedish registry study of 778 cases. Obstet Gynecol. 1991;77(6):835.
43. Abbasi N, Patenaude V, Abenhaim HA. Management and outcomes of acute appendicitis in pregnancy-population-based study of over 7000 cases. BJOG. 2014;121(12):1509.
44. Birnbaum BA, Wilson SR. Appendicitis at the millennium. Radiology. 2000;215(2):337.
45. Richards C, Daya S. Diagnosis of acute appendicitis in pregnancy. Can J Surg. 1989;32(5):358.

46. Smith MP, Katz DS, Lalani T, Carucci LR, Cash BD, Kim DH, Piorkowski RJ, Small WC, Spottswood SE, Tulchinsky M, Yaghmai V, Yee J, Rosen MP. ACR appropriateness criteria® right lower quadrant pain--suspected appendicitis. Ultrasound Q. 2015;31(2):85–91.
47. Kastenberg ZJ, Hurley MP, Luan A, Vasu-Devan V, Spain DA, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of preoperative imaging for appendicitis after indeterminate ultrasonography in the second or third trimester of pregnancy. Obstet Gynecol. 2013;122(4): 821–9.
48. Theilen LH, Mellnick VM, Longman RE, Tuuli MG, Odibo AO, Macones GA, Cahill AG. Utility of magnetic resonance imaging for suspected appendicitis in pregnant women. Am J Obstet Gynecol. 2015;212(3):345.e1–6.
49. Ellington SR, Flowers L, Legardy-Williams JK, Jamieson DJ, Kourtis AP. Recent trends in hepatic diseases during pregnancy in the United States, 2002–2010. Am J Obstet Gynecol. 2015;212(4):524.e1.
50. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? JAMA. 2003;289(1):80.
51. Sousa I, Fernandes A, Távora I. Emphysematous cholecystitis: imaging diagnosis of an emergent condition. Acta Med Port. 2016;29(11):761.
52. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc. 1992;40(11):1100.
53. Fulop M, Tannenbaum H, Dreyer N. Ketotic hyperosmolar coma. Lancet. 1973;2(7830):635.
54. Arieff AI, Carroll HJ. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. Medicine (Baltimore). 1972;51(2):73.
55. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev. 1999;15(6):412–26.
56. Sheikh-Ali M, Karon BS, Basu A, Kudva YC, Muller LA, Xu J, Schwenk WF, Miles JM. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care. 2008;31(4):643–7.
57. Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG. Thyrotoxicosis complicating pregnancy. Am J Obstet Gynecol. 1989;160:63–70.
58. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. Obstet Gynecol. 1994;84:946–9.
59. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010;31(5):702.
60. Lo JC, Rivkees SA, Chandra M, Gonzalez JR, Korelitz JJ, Kuzniewicz MW. Gestational thyrotoxicosis, antithyroid drug use and neonatal outcomes within an integrated healthcare delivery system. Thyroid. 2015;25(6):698–705.
61. Ecker JL, Musci TJ. Thyroid function and disease in pregnancy. Curr Probl Obstet Gynecol Fertil. 2000;23:109–22.
62. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 37, August 2002. (Replaces Practice Bulletin Number 32, November 2001). Thyroid disease in pregnancy. Obstet Gynecol. 2002;100(2):387.
63. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman W, Laurberg P, Lazarus JH, Mandel SJ, Peeters R, Sullivan S. Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2016;27(3):315–89.
64. Patterson TF, Andriole VT. Detection, significance, and therapy of bacteriuria in pregnancy. Update in the managed health care era. Infect Dis Clin North Am. 1997;11(3):593.
65. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM, Infectious Diseases Society of America, American Society of Nephrology, American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40(5):643.

66. Gilstrap LC 3rd, Ramin SM. Urinary tract infections during pregnancy. Obstet Gynecol Clin N Am. 2001;28(3):581.
67. Harris RE, Gilstrap LC 3rd. Cystitis during pregnancy: a distinct clinical entity. Obstet Gynecol. 1981;57(5):578.
68. Hill JB, Sheffield JS, McIntire DD, Wendel GD Jr. Acute pyelonephritis in pregnancy. Obstet Gynecol. 2005;105(1):18.
69. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. Am J Obstet Gynecol. 2014;210(3):219.e1–6.
70. Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and practice of infectious diseases, 7, vol. 1. Philadelphia: Elsevier; 2010. p. 957.
71. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA. 2002;287(20):2701.
72. Fairley KF, Carson NE, Gutch RC, Leighton P, Grounds AD, Laird EC, McCallum PH, Sleeman RL, O'Keefe CM. Site of infection in acute urinary-tract infection in general practice. Lancet. 1971;2(7725):615.
73. Wing DA, Hendershott CM, Debuque L, Millar LK. A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. Obstet Gynecol. 1998;92(2):249.
74. Fulop T. Acute pyelonephritis treatment and management. 2016. http://emedicine.medscape.com/. Accessed 27 Feb 2017.
75. Bischoff SC, Renzer C. Nausea and nutrition. Auton Neurosci. 2006;129(1–2):22.
76. Erick M. No more morning sickness: a survival guide for pregnant women. New York: Plume; 1993.
77. Newman V, Fullerton JT, Anderson PO. Clinical advances in the management of severe nausea and vomiting during pregnancy. J Obstet Gynecol Neonatal Nurs. 1993;22(6):483.
78. Koretz RL, Rotblatt M. Complementary and alternative medicine in gastroenterology: the good, the bad, and the ugly. Clin Gastroenterol Hepatol. 2004;2(11):957.
79. Schwertner HA, Rios DC, Pascoe JE. Variation in concentration and labeling of ginger root dietary supplements. Obstet Gynecol. 2006;107(6):1337.
80. Roscoe JA, Matteson SE. Acupressure and acustimulation bands for control of nausea: a brief review. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S244.
81. Bender DA. Non-nutritional uses of vitamin B6. Br J Nutr. 1999;81(1):7–20.
82. Gdynia HJ, Müller T, Sperfeld AD, Kühnlein P, Otto M, Kassubek J, Ludolph AC. Severe sensorimotor neuropathy after intake of highest dosages of vitamin B6. Neuromuscul Disord. 2008;18(2):156–8.
83. Koren G, Hankins GD, Clark S, Caritis SN, Miodovnik M, Umans JG, Mattison DR. Effectiveness of doxylamine-pyridoxine for morning sickness. Am J Obstet Gynecol. 2016;214(5):664–6.
84. Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, Mattison DR. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010;203(6):571.e1.
85. Mazzotta P, Magee LA. A risk-benefit assessment of pharmacological and nonpharmacological treatments for nausea and vomiting of pregnancy. Drugs. 2000;59(4):781–800.
86. Gilboa SM, Strickland MJ, Olshan AF, Werler MM, Correa A, National Birth Defects Prevention Study. Use of antihistamine medications during early pregnancy and isolated major malformations. Birth Defects Res A Clin Mol Teratol. 2009;85(2):137–50.
87. Li Q, Mitchell AA, Werler MM, Yau WP, Hernández-Díaz S. Assessment of antihistamine use in early pregnancy and birth defects. J Allergy Clin Immunol Pract. 2013;1(6):666–74.e1.
88. Yerushalmy J, Milkovich L. Evaluation of the teratogenic effect of meclizine in man. Am J Obstet Gynecol. 1965;93(4):553.
89. Milkovich L, van den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. Am J Obstet Gynecol. 1976;125(2):244.
90. Shapiro S, Kaufman DW, Rosenberg L, Slone D, Monson RR, Siskind V, Heinonen OP. Meclizine in pregnancy in relation to congenital malformations. Br Med J. 1978;1(6111):483.

91. Einarson A, Koren G, Bergman U. Nausea and vomiting in pregnancy: a comparative European study. Eur J Obstet Gynecol Reprod Biol. 1998;76(1):1.
92. Pasricha PJ, Pehlivanov N, Sugumar A, Jankovic J. Drug Insight: from disturbed motility to disordered movement—a review of the clinical benefits and medicolegal risks of metoclopramide. Nat Clin Pract Gastroenterol Hepatol. 2006;3(3):138.
93. Fitzgerald JP. The effect of promethazine in nausea and vomiting of pregnancy. N Z Med J. 1955;54(300):215.
94. Klauser CK, Fox NS, Istwan N, Rhea D, Rebarber A, Desch C, et al. Treatment of severe nausea and vomiting of pregnancy with subcutaneous medications. Am J Perinatol. 2011;28:715–21.
95. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med. 2013;368:814–23.
96. Safari HR, Alsulyman OM, Gherman RB, Goodwin TM. Experience with oral methylprednisolone in the treatment of refractory hyperemesis gravidarum. Am J Obstet Gynecol. 1998;178(5):1054.
97. McParlin C, O'Donnell A, Robson SC, Beyer F, Moloney E, Bryant A, Bradley J, Muirhead CR, Nelson-Piercy C, Newbury-Birch D, Norman J, Shaw C, Simpson E, Swallow B, Yates L, Vale L. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review. JAMA. 2016;316(13):1392–401.
98. Shepard TH, Brent RL, Friedman JM, Jones KL, Miller RK, Moore CA, Polifka JE. Update on new developments in the study of human teratogens. Teratology. 2002;65(4):153.
99. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet. 1999;86(3):242.
100. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, Diav-Citrin O, Chitayat D, Nulman I, Einarson TR, Koren G. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000;62(6):385.
101. Rodríguez-Pinilla E, Martínez-Frías ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology. 1998;58(1):2.
102. Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P. Contributors to the MADRE database. First trimester exposure to corticosteroids and oral clefts. Birth Defects Res A Clin Mol Teratol. 2003;67(12):968.
103. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. Ann Epidemiol. 2003;13(5):317.
104. Dombrowski MP, Schatz M, Wise R, Momirova V, Landon M, Mabie W, et al. Asthma during pregnancy. National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network and the National Heart, Lung, and Blood Institute. Obstet Gynecol. 2004;103:5–12.
105. Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network; National Heart, Lung, and Blood Institute. Am J Obstet Gynecol. 2006;194:120–6.
106. Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. Immunol Allergy Clin N Am. 2006;26(1):63–80.
107. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed 12 May 2011.
108. Charlton RA, Snowball JM, Nightingale AL, Davis KJ. Safety of fluticasone propionate prescribed for asthma during pregnancy: A UK population-based cohort study. J Allergy Clin Immunol Pract. 2015;3(5):772–779.e3.

109. Cossette B, Beauchesne MF, Forget A, Lemière C, Larivée P, Rey E, Blais L. Relative perinatal safety of salmeterol vs formoterol and fluticasone vs budesonide use during pregnancy. Ann Allergy Asthma Immunol. 2014;112(5):459–64.
110. Cossette B, Forget A, Beauchesne MF, Rey É, Lemière C, Larivée P, Battista MC, Blais L. Impact of maternal use of asthma-controller therapy on perinatal outcomes. Thorax. 2013;68(8):724–30.
111. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol. 2003;102(4):739.
112. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD, Organization Of Teratology Information Services Research Group. Asthma medication use in pregnancy and fetal growth. J Allergy Clin Immunol. 2005;116(3):503.
113. Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. J Allergy Clin Immunol. 1986;78(2):349.
114. Schatz M, Patterson R, Zeitz S, O'Rourke J, Melam H. Corticosteroid therapy for the pregnant asthmatic patient. JAMA. 1975;233(7):804.
115. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. (NIH publication no. 08-4051). www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed 04 Dec 2014.
116. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). www.ginasthma.org. Accessed 10 June 2016.
117. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. J Allergy Clin Immunol. 2005;115(1):34.
118. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, ESC Committee for Practice Guidelines. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147.
119. Alwan S, Polifka JE, Friedman JM. Angiotensin II receptor antagonist treatment during pregnancy. Birth Defects Res A Clin Mol Teratol. 2005;73(2):123.
120. Lavoratti G, Seracini D, Fiorini P, Cocchi C, Materassi M, Donzelli G, Pela I. Neonatal anuria by ACE inhibitors during pregnancy. Nephron. 1997;76(2):235.
121. Schubiger G, Flury G, Nussberger J. Enalapril for pregnancy-induced hypertension: acute renal failure in a neonate. Ann Intern Med. 1988;108(2):215.
122. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Papp Z, Mouquet F, McMurray JJ, Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail. 2010;12(8):767.
123. NIH. U.S. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACTMED. Accessed 01 July 2014.

124. Beardmore KS, Morris JM, Gallery ED. Excretion of antihypertensive medication into human breast milk: a systematic review. Hypertens Pregnancy. 2002;21(1):85.
125. Lindheimer MD, Katz AI. Sodium and diuretics in pregnancy. N Engl J Med. 1973; 288(17):891.
126. Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/docs/2014-138/pdfs/2014-138.pdf. Accessed 23 Mar 2017.
127. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688.
128. Cosmi B, Hirsh J. Low molecular weight heparins. Curr Opin Cardiol. 1994;9(5):612.
129. Litin SC, Gastineau DA. Current concepts in anticoagulant therapy. Mayo Clin Proc. 1995;70(3):266.

Part III
The Opioid Epidemic: Tools for the Hospitalist

1.1 Introduction

America's Opioid epidemic may be the most significant event to face hospital medicine since its inception. Appropriately an entire section of this text is dedicated to that topic. The epidemic poses a multitude of complex challenges that cross over to many specialties. In this context hospital medicine with its broad understanding and interaction with all specialties may be best suited to address the issues. However, hospitalist may find it difficult to interact with healthcare systems that have only valued them for their clinical in-patient skills. Whatever the challenges, the issues are simply too large for many to ignore.

There are no simple solutions to this problem that in many ways has been self-inflicted by the financial incentives of the healthcare system. Hospital medicine is called upon to not only effectively respond to the epidemic but also to provide urgently needed leadership. In many healthcare systems this is occurring. The following four chapters address the origins of the epidemic, the pathophysiology, the clinical implications, and the development of tools both from an individual practitioner and from a system standpoint. I hope this serves as good primer for all hospitalists and would be interested to hear about the challenges faced in your own programs and how hospitalists have been a part of the solution.

Chapter 13
Solving America's Prescription Epidemic: Pathophysiology, Ethics, Chronic Pain, and Addiction

Marianne Maumus

Introduction

In 2007, 12.5 million Americans used prescription opioids for nonmedical reasons [1]. In 2013, 16,235 Americans died from prescription opioid misuse [2]. Prescription opioid misuse affects populations that are not traditionally thought of as drug seeking. Individuals who overdose are more likely to be white, female, and middle-aged [2]. In addition, the abuse of prescription opioids is tightly linked to heroin use [2]. Abuse of prescription opioids increases the risk of heroin use by a factor of 40, and 45% of heroin users are also addicted to opioid pain medication.

The opioid epidemic is cultural pestilence that is exclusively an American phenomenon. The cardinal features of this epidemic include diversion of tablets, chronic pain, addiction, psychiatric illness, and overutilization of healthcare resources. These cardinal features are relate to one another via human brain anatomy, physiology, and function and American culture. These cardinal features reinforce one another, causing psychopathology and pain—both in the individual and throughout the community (see Table 13.1).

For many years, the ill effects of opioids have been well known and documented. The history of opioids began in 1806 when the German chemist Friedrich Wilhelm Sertürner isolated morphine from opium. During the American Civil War, morphine was used as a pain killer. In the post-Civil War period, addiction was prevalent and became known as Soldier's Disease. In 1898, the German chemical company Bayer synthesized, produced, and marketed heroin as a nonaddictive alternative to morphine. In 1909, the US Congress passed the Opium Exclusion Act, which barred the importation of opium for the purpose of smoking. The 1914 Harrison Tax Act required physician and pharmacist registration for the distribution of opiates. That

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Table 13.1 Cardinal features of the opioid epidemic

• Diversion of tablets
• Chronic pain
• Addiction
• Psychiatric illness
• Overutilization of healthcare resources

same year, Kennedy Foster wrote in the *New York Medical Journal*, "Morphinism is a disease, in the majority of cases, initiated, sustained and left uncured by members of the medical profession" [3].

Taking an opioid can change a person's life trajectory without his/her awareness. Opioids quickly dominate the brain's neurochemistry to alter judgment and behavior, cause permanent anatomic and functional changes to neural circuits, and start a cascading series of unfortunate events.

Rather than viewing chronic pain, opioid dependence, and related psychiatric disease as a one-time event in a patient's life, these conditions should be considered together and treated as a chronic and relapsing illness. This is a single disease that deserves a comprehensive chronic disease management strategy, one that is team based and patient centered. Only with a compassionate commitment to serving the health needs of a population will healthcare systems of the future be able to improve quality, reduce cost, align values and incentives, engage patients, and ultimately reduce morbidity and mortality. These chapters build the fundamental knowledge base required to meet these goals.

Opioids and the Brain

Opioids directly impair important structures of areas in the brain that control judgment, memory formation, regulation of pain, and emotional control. These structures include the prefrontal cortex, nucleus accumbens, ventral tegmental area, amygdala, rostral ventral medulla, and periaqueductal grey zone. Opioids also affect microglial cell function of the brain and spinal cord and many other important connecting neural pathways and nuclei.

The Unconscious Brain

Proper functioning of the unconscious brain is vital for the well-being of the individual and the community. Ninety-five percent of the human brain controls the unconscious mind. Only 5% of brain tissue involves conscious thought processes. Thirty percent of the unconscious mind handles and processes vision. According to Immanuel Kant, the unconscious mind does not merely document objective events

but actively constructs a picture of the world. Research has demonstrated that when information is incomplete, the unconscious brain fills in the blanks and actively reshapes memory continuously. The unconscious mind is automatic and has knowledge unknown to the conscious mind.

Therefore, two distinct trains of mental action are taking place simultaneously, both conscious and unconscious. While the conscious mind attempts to play the role of the objective seeker of the truth, the unconscious mind is the impassioned advocate for what we want to believe. When we assess ourselves internally, we produce a positive picture. People's views are highly correlated to their vested interest, and the mind is programmed to opt for happiness. When making decisions, people are likely to make the irrational choice in order to maintain happiness. *Motivated reasoning* is a theoretical construct that explains how unconscious processes help the human to believe in his/her goodness, to feel in control, to see him/herself in a positive light, to interpret his/her social environment, and to defend against unhappiness. It provides the human strength to overcome obstacles. Research has demonstrated that motivation affects perception [4].

Two systems of the unconscious brain that are affected by opioids include the learning reward system and the pain matrix. The learning reward system controls Pavlovian learning and pleasure and connects intimately to areas that control judgment, memory formation, and emotional control. Over time with exposure to opioids, the learning reward system turns into the addiction pathway that regulates drug-related behavior. Opioids usurp the normal learning and emotional control pathways, causing impulsive and drug-seeking behaviors and the formation of permanent drug-related memories [5]. These memories are formed by intracellular, genetic, and anatomic changes that alter nerve function and tip the balance of motivated learning from natural rewards toward drug-associated regulative relapse (conscious memory circuit) and then toward unconscious compulsive relapse (habit circuitry) [5].

The pain matrix is that part of the brain that processes nociceptive stimuli. It has a 3-tiered processing system that involves the attention/perception areas of the cerebral cortex and the reappraisal/emotional areas of the prefrontal and frontal lobe [6]. The learning reward system converts to the addiction pathway with exposure to opioids and is anatomically and functionally connected to the pain matrix. To explore the relationship between the two neurologic systems in greater depth requires an understanding of both the brain disease model of dependence and addiction and the pain matrix.

Brain Disease Model of Dependence and Addiction

The brain disease model of dependence and addiction is based on neuropsychopharmacology research as outlined over many years in the scientific literature [5, 7]. Dependence and addiction are not separate disease processes but rather are a continuum of pathology that progresses with ongoing use of the offending substance [5].

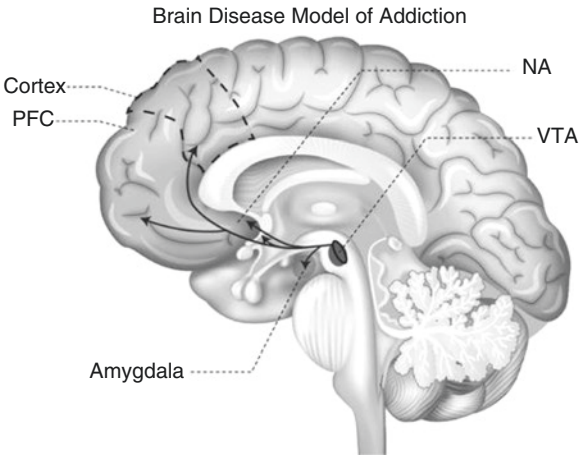

Fig. 13.1 Brain disease modal of addiction. *PFC* prefrontal cortex, *NA* nucleus accumbens, *VTA* ventral tegmental area

A detailed review of the pathology of staged neuroplasticity (lasting change to the brain) of addiction is included in the reference list [5], but a simple explanation that can be used for patient education is presented here (Fig. 13.1).

The ventral tegmental area and the nucleus accumbens are the learning and pleasure centers of the brain, the location of Pavlovian learning. It makes sense that pleasure and learning would be together in normal circumstances. To stimulate remembrance, a pleasure signal entices the human to repeat the action. When a person learns something new, there is a dopamine flash in these two areas, followed by a weak dopamine signal to the prefrontal cortex. Dopamine release in the prefrontal cortex begins to make connections with cortical nerve fibers to create memory and to provide feedback loops to the amygdala, the emotional center of the brain. The amygdala is not mature until age 24. Without prefrontal control, the amygdala tips the balance of behavior toward impulsive actions [5, 7].

With opioids, there is a dopamine blast instead of a healthy pleasurable flash. Euphoria is the result. The brain responds with several adaptive changes, both intracellular and within the synapse, depending on the drug. The net effect is the same: to reduce the effect of dopamine in the ventral tegmental area and nucleus accumbens so that more drug is needed to get the same effect. A dopamine blast also travels up to the prefrontal cortex, and dopamine is released excessively between the cortical and precortical nerve fibers. The adaptive response is the receding of affected neuron dendrites there, thus halting normal memory formation and disconnecting control over the amygdala. Inability to achieve academically, progressive psychiatric disorders, and lack of impulse control are the result [5, 7].

The brain disease model of dependence and addiction is fully established in science and is not a theory. The development of enduring neuroplasticity is supported by neuroimaging with functional MRI scans, by direct visualization of a reduction of prefrontal cortical measures of metabolism and blood flow and reduced striatal

levels of dopamine D2 receptors in addicted individuals [5]. These permanent changes are called *hypofrontality* and include regions such as the anterior cingulate and ventral orbital cortex [5]. The capacity for biologically relevant stimuli to activate the prefrontal cortex has been shown to be impaired in patients formerly exposed to prolonged opioids, yet drug-associated stimuli continue to markedly activate the prefrontal cortex [5]. Neuroimaging data provide a neurocircuitry template for the prime features of addiction [5]. The role of dopamine changes from one of promoting new learning to one of enabling the use of learned information to efficiently execute the adaptive behavioral response. Behavior evolves from being a declarative process into a habitual behavior utilizing working memory circuits [5]. This change allows a transition from declarative to automatic behaviors that proceed without conscious control and cause compulsive relapse [5]. The capacity of prefrontal, declarative circuitry to intrude on and disrupt the drug-seeking habit also becomes impaired [5]. In animal models, enduring neuroplasticity has been demonstrated in the cortical glutamate circuitry, identifying habit circuitry in the dorsolateral striatum, regardless of the modality or the drug used to induce drug-seeking behavior [5]. In summary, adaptive changes that occur early in the disease progression promote behaviors toward addiction but can resolve with abstinence. Later in the disease, habit circuitry is established and is permanent.

Lack of behavioral control is a pharmacologically induced phenomenon [5]. Addiction is a progression of brain pathology [5]. There is a hierarchy of events, a 3-tiered progression that occurs [5]. Physiologically, addiction progresses from intracellular changes, to changes in anatomy and function of neural circuits, to establishment of permanent unconscious behaviors and drug-related memories [5]. Clinically, addiction progresses from first exposure to conscious dependence to loss of unconscious control [5]. Because neuroplasticity leads to permanent drug-associated memories, addiction should be viewed as a chronic relapsing disease, not as an acute episodic illness.

The Pain Matrix

The pain matrix includes the parts of the brain that control and modulate sensory input that comes from the dorsolateral spinothalamic tracts of the spinal cord. The pain matrix consists of a constellation of brain regions, a multilevel hierarchical neural network, and the sensory input creates a pattern of neural activation that represents the *pain signature* of the experience. Sensory information is continuously streaming in, and the brain has to interpret it, place meaning onto it, and then reflect it back to the original source [6].

1. First, the nociceptive input data arrives to the thalamus (Fig. 13.2).
2. Then it is interpreted in the perceptual-attentional areas of the cortex. This is conscious modulation (Fig. 13.3).

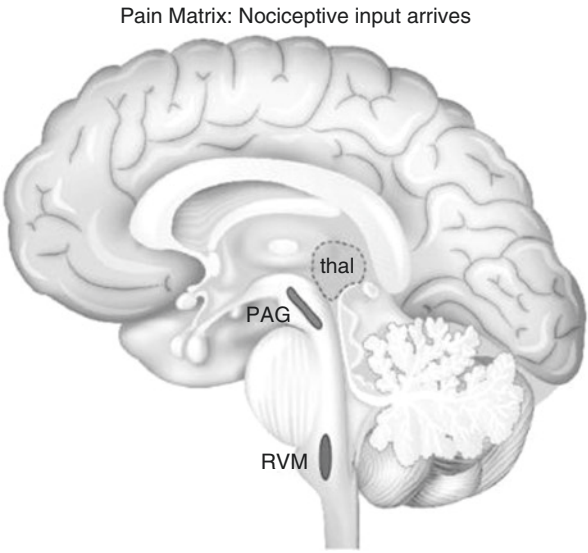

Fig. 13.2 Pain matrix: nociceptive input arrives. *PAG* periaqueductal grey zone, *RVM* rostral ventral medulla, *thal* thalamus

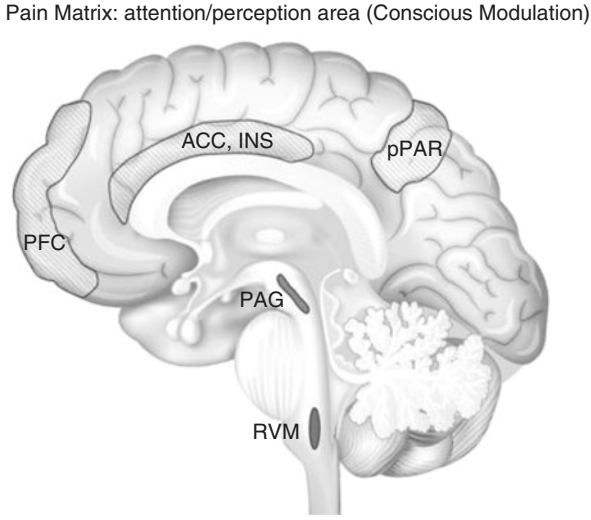

Fig. 13.3 Pain matrix: attention/perception areas (conscious modulation). *ACC, INS* anterior cingulate cortex, insula, *pPAR* posterior parietal lobe, *PFC* prefrontal cortex, *PAG* Periaqueductal grey zone, *RVM* rostral ventral medulla

3. Then the nociceptive input is reflected into the reappraisal-emotional areas so that importance can be applied to the information. This is unconscious modulation (Fig. 13.4).

After the sensory input is altered by these three filters, descending modulation of the pain signature occurs. The pain signature enters the periaqueductal grey zone and can be inhibited or facilitated, either toning down the pain response or increasing it. Here, there is a high concentration of opioid receptors [8]. Then the altered signature enters the rostral ventral medulla, which contains *on cells* and *off cells*,

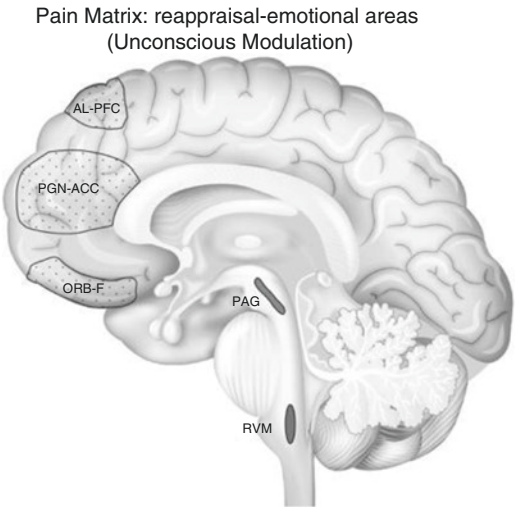

Fig. 13.4 Pain matrix: reappraisal-emotional areas (unconscious modulation). *AL-PFC* anterior lateral prefrontal cortex, *PGN-ACC* perigenual anterior cingulate cortex, *ORB-F* orbital frontal lobe, *PAG* periaqueductal grey zone, *RVM* rostral ventral medulla

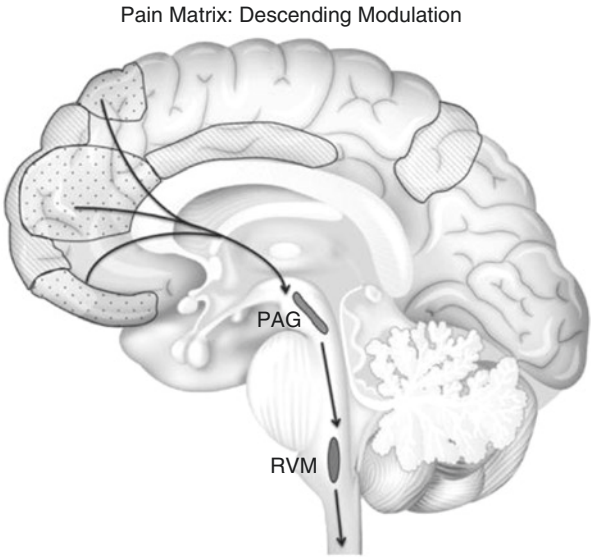

Fig. 13.5 Pain matrix: descending modulation. *PAG* periaqueductal grey zone, *RVM* rostral ventral medulla

before it passes back to the dorsal horn and reflects back to the original source [8]. These midbrain structures are analogous to the volume control and the light switch for pain in the midbrain. Normally, after the pain signature is reflected back to the original source, in the brain it deintensifies with time and distraction (Fig. 13.5).

The learning reward system and pain matrix are connected by overlapping neural networks. These anatomic regions are located in the conscious and unconscious mind. Connectivity mainly occurs between the medial prefrontal cortex and the nucleus accumbens. Prefrontal brain regions are involved in the inhibition of

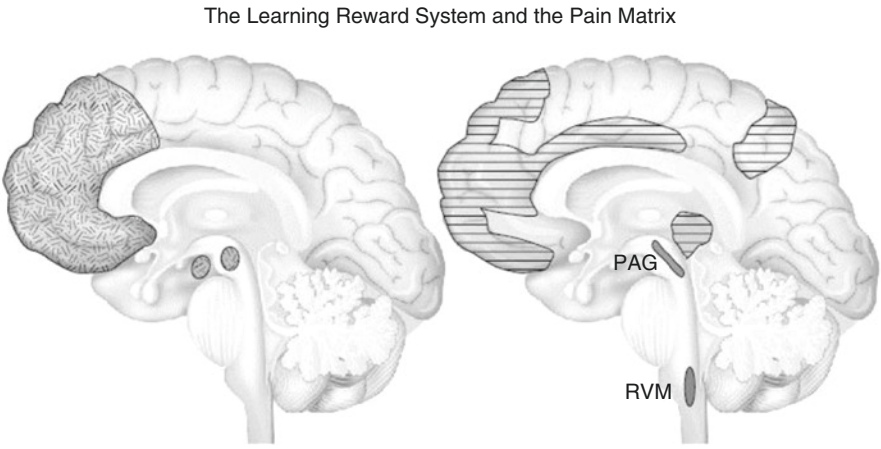

Fig. 13.6 The learning reward system and the pain matrix. *PAG* periaqueductal grey zone, *RVM* rostral ventral medulla

Table 13.2 Effect of opioids onto the brain

Opioids intensify neuroinflammation in the periaqueductal gray zone, the rostral ventral medulla, and the dorsal horn, causing central sensitization
Opioids reinforce the memory of the pain matrix signatures

nociception as well as in the transition from declarative memories to habitual working memory circuits [5, 8]. The periaqueductal grey zone sits right next to the ventral tegmental area and receives input from the prefrontal cortex, insula, and other important structures. It makes sense that the systems for human learning and pain are intimately connected. It is obvious that learning to avoid painful events would deter risky behavior, promote the seeking of healthy and safe environments, and stimulate cooperation within human communities (Fig. 13.6).

Opioids work by turning off the reflection of the pain signature at the level of the periaqueductal grey zone and rostral ventral medulla [9]. Opioids block the function of on cells and stop transition of the pain signature through the rostral ventral medulla. Regrettably, opioids also cause the release of cytokines, interleukins, and glutamate from microglial cells, which are resident macrophages in the brain. They intensify neuroinflammation in these areas, leading to cell death and cell dysfunction. Opioids also have been shown to disrupt the function of glial cells in the brain and in the dorsal horn of the spinal cord, causing spontaneous firing of neurons and leading to hyperalgesia and chronic pain [9]. The pain associated with neuroinflammation is termed *central sensitization.*

At the same time that opioids block the pain signature in the midbrain, opioids also intensify the pleasure signal by stimulating the ventral tegmental area and the nucleus accumbens [5] (Table 13.2). Opioids reinforce the memory of the pain matrix signature by increasing dopamine in the nucleus accumbens and ventral tegmental area, thus increasing the pleasure signal at the same time as the painful

event. When the effect of the opioids wears off, the periaqueductal grey zone and rostral ventral medulla release the signal, the pleasure signal also disappears, and the patient's pain perception gets worse. These two key physiologic events trigger intense fear and avoidance behaviors that clinically manifest as behavior called *pain catastrophizing*, described in the biopsychosocial model of pain [6]. Pain catastrophizing is the anticipation of the worst possible outcome and focuses attention on pain and related symptoms [6]. With repeated use of opioids, all the maladaptive neuroplastic changes that were seen in the addiction pathway progress over time, adversely affecting prefrontal cortex control over both the amygdala and the periaqueductal grey zone, strengthening habit circuitry, and leading to highly emotional patients in constant pain.

Psychiatric Disorders: Shared Neural Networks

True story: A 52-year-old woman with a 5-year history of uncontrolled migraine headaches and anxiety presented to the hospital. She had a history of recurrent admissions for the same diagnosis. She is followed by a neurologist, who has tried all the usual pharmacotherapies and all alternative therapies. The patient has also been treated with opioids, in particular with Dilaudid (hydromorphone) during hospital admissions and oxycodone in the outpatient setting. The hospital staff (nurses, residents, staff physicians) were in distress because of their inability to relieve her pain, which was severe. She was admitted to the ICU and a trial of sedation with IV propofol was attempted. After treatment, the patient woke up with a headache. A new staff rotated onto the service, and all therapies were discontinued. The patient remained in bed with her head under a pillow for 3 days. She was kept on maintenance fluids, and nausea was treated with Zofran (ondansetron). On the fourth day, she was found sitting on the side of the bed eating breakfast, and she requested to go home. At discharge, she was instructed not to take anything for her headaches. Four months later, she expressed gratitude because her headaches were still resolved.

For this patient, it is clear that prescribing behaviors were dictated by her anxiety. Unrecognized pain catastrophizing increased the desire of providers who had empathy for their patient to provide short-term relief (Table 13.3). There was a gradual increase in opioid prescriptions over a prolonged period due to progressive symptoms and possibly to opioid-induced drug-seeking behavior. Central sensitization resulting from opioid use became the main source of the patient's pain over time and manifested as the original location of her pain, which was migraine headache. Ideally, the patient should have been treated with antiseizure medication, a tricyclic antidepressant, and a serotonin-norepinephrine reuptake inhibitor to manage central

Table 13.3 Pharmacologic treatment for central sensitization (brain pain)

• Neurontin (gabapentin) 100–300 mg tid
• Trazodone 25–50 mg qhs
• Cymbalta (duloxetine), 20 mg bid

Table 13.4 Personality disorders

• *Borderline*—Impulsivity, instability in relationships
• *Narcissistic*—Grandiosity, need for admiration, lack of empathy
• *Dependent*—Submissive, excessive care needs
• *Histrionic*—Excessive emotionality and attention seeking
• *Obsessive-Compulsive*—Excessive orderliness, perfectionism, and control

sensitization and anxiety and to remove the offending drug. She should have been counseled that a transition period of opioid withdrawal was required, kept in the hospital due to the severity of her symptoms, and placed into a functional restoration program upon discharge to prevent relapse.

Chronic pain and psychiatric disorders have shared neural mechanisms. The relationship between chronic pain and psychiatric illness is bidirectional [6]. Chronic pain leads to depression, and depression leads to chronic pain [6]. There is also a bidirectional relationship between patients with migraine headache and anxiety disorders [6]. Evidence for this is based on functional MRI imaging studies and epidemiologic studies [6]. Chronic pain leads to substance use disorders, and substance use disorders, including cannabis use, lead to chronic pain [6]. Additionally, suicide risk factors have increased prevalence among patients with chronic pain [6]. Sexual violence is a known risk factor for the development of chronic pain, irritable bowel syndrome, and psychogenic seizures [6]. Patients with personality disorders and neuroticism (negative thoughts) have increased sensitivity to pain, greater disability, and a lower quality of life [6].

The associations between chronic pain and psychiatric disorders are well described in the medical literature [6]. The fact that opioids affect the modulation of pain and lead to central sensitization and addiction is also widely accepted. The three conditions—chronic pain, psychiatric disorders, and addiction—are intimately entwined in the brain. Even though attempts have been made to classify them by diagnostic-related groups, they cannot be separated in the body in clinical practice. They must be considered the same disease process and treated together. With persistent use of opioids, acute pain progresses to chronic pain, then to conscious opioid dependence, and last to unconscious addiction. Prolonged fear coupled with prefrontal lobe dysfunction progresses to chronic anxiety, other psychopathology, and the development of personality disorders (Table 13.4).

The biopsychosocial model of pain conceptualizes the interrelationship between biological factors, psychological processes, and social influences [6]. The fear and avoidance model, which is within the biopsychosocial model, is a widely accepted theoretical construct used to explain how psychological processes mediate the transition of acute episodic pain to chronic pain [6]. The primary factor is fear that leads to negative cognitions [6]. Fear and avoidance beliefs are the key drivers of pain-related disability. Research with functional MRI imaging studies supports the fear and avoidance model [6]. Treatment includes cognitive-behavioral therapy, acceptance-based therapies, multidisciplinary pain rehabilitation, and psychopharmacological treatments [6].

Ethics: Autonomy and the Unconscious Brain

True story: A 32-year-old male presented to the ED with history of Crohn disease. He was a Gulf War veteran who was discharged from the army for uncontrolled "symptoms." He was unable to get relief of his symptoms at Walter Reed Hospital in Washington, DC, so he left that hospital and tried hospitals in every state along the East Coast until he finally landed at a newly opened post-Katrina hospital in New Orleans. He was admitted and discovered to have factitious diarrhea, induced by taking magnesium citrate in his hospital room. Advice was given to seek help for post-traumatic stress disorder (PTSD) and addiction, causing him to leave against medical advice. He returned 2 weeks later with a large open scar on his abdomen. Upon questioning, he reported that he caught a military cargo plane from Washington, DC, to Frankfort, Germany, where surgeons removed part of his colon. After surgery, the wound "popped open," so he came home. Later, he admitted to pulling the wound open in order to convince the surgeons to give him more Dilaudid (hydromorphone). Again, upon admission, proper treatment for PTSD and addiction was recommended, and he agreed. Surgery was consulted for proper wound care. He was withdrawn from opioids over 5 days and sent back to Walter Reed for ongoing psychiatric and addiction care.

The above case demonstrates a healthcare system that is not empowered to rescue the addicted patient in need. The patient obviously had poor judgment, and healthcare providers lacked legal means to secure the patient in a safe environment. He was unable to make correct choices about his healthcare needs and thus was doomed to escalate his condition. In this case, multiple healthcare facilities either failed to identify the addictive disorder, quietly chose to ignore it, or exacerbated the problem with a misdiagnosis *or* the patient ignored good advice and moved on to the next hospital. There continues to be poor communication between hospitals and lack of an organized approach and plan for the patient who doctor-shops.

Understanding the pathophysiology of addiction and pain raises an important ethics question. With the alteration of brain structures that control pleasure, pain, Pavlovian learning, personality, judgment, memory formation, motivation, and emotional control, can a patient exposed to opioids even have autonomy? Autonomy is defined as the ability of a person to make his/her own decisions. Proper cognition requires both the conscious and unconscious components of the brain to work together. Does a patient, after unconscious brain structures have been altered or even damaged by opioids, have the ability to make rational choices? In other words, can a patient have voluntary control of his/her behavior once the biologic control of that behavior is tipped toward irrationality and impulsivity by a drug? If physicians gave a drug that treated pain effectively and also took away vision, would we expect that patient to be able to read? How then, can we give a patient a substance that affects judgment, pleasure, motivation, and emotional control and then expect that patient to be able to make reasonably correct decisions? Who would be responsible for the blind patient's future educational advancement and employability once he/she is no longer able to read? Who then, is responsible for the impulsive behavior of the patient exposed to opioids?

The ethical principle of autonomy is often used to justify the ongoing prescribing of opioids to patients who complain of pain. However, it is well known that patients in distress are not always capable of making the correct decision about their care, especially in an emergency or in a painful state. It takes a mature, brave, knowledgeable, compassionate, and committed physician to take control and remove the patient from the emergency, or in the case of opioid dependence, from the offending substance. The notion that patients can have autonomy and altered brain function at the same time is wrong. Such thinking ignores the brain disease model of dependence and addiction and does not correlate with basic understanding of the unconscious mind and how important the unconscious mind is for controlling human decision-making and behavior. Also, this notion is flawed because it does not recognize chronic pain as a distinct disease entity affecting the unconscious brain, and it does not recognize the pharmacologic assault that takes place on unconscious brain structures when opioids are taken. The concept of autonomy is dependent on a well-functioning brain, including both the conscious and the unconscious mind.

Addicted patients can appear to be powerful self-advocates, even though they are self-destructive. Autonomy is not equivalent to capacity, which is a conscious process that requires a functioning temporal lobe and the ability to understand and verbalize wishes regarding care. Capacity is a legal definition, and the patient must have capacity to provide consent for a medical procedure or a treatment. However, capacity has no role in the determination of the appropriateness of a certain procedure or a treatment. Capacity evaluations were not meant to guide physician prescribing, even with highly verbal, threatening, and emotional patients who want opioids. The definition of capacity omits the unconscious brain as an important part of cognitive function. When considering opioid therapy, a thorough evaluation of a patient's unconscious behavior is needed to determine autonomy, and autonomy cannot be assumed. The provider can evaluate a patient's unconscious behavior by observing and documenting aberrant behaviors over time in serial clinical settings. A history of irrational actions and loss of behavioral control is supporting evidence. Frequently, patients who have progressed to opioid dependence have lost unconscious control, but they still have enough conscious function to maintain capacity. A unique clinical observation is that they can be sincere and unreliable at the same time. Providers need to take care to avoid the assumption that capacity equals autonomy, because this assumption places the patient in a vulnerable situation with a lack of protection when he/she becomes opioid dependent (Table 13.5).

One could argue that patients who have alteration of their unconscious brain structures do not have the right to dictate their care. If one has an injured temporal lobe that affects capacity or consciousness, a power of attorney is required to make decisions. Patients with injury to their unconscious brain structures also need oversight of their behavior and decision-making. The word *dependent* suggests that a

Table 13.5 Hallmarks of opioid dependency or addiction

• Sincere and unreliable at the same time
• History of loss of behavioral control
• Presence of aberrant behavior

guardian is needed, implying a lack of self-governance. A proper caregiver co-manager, preferably a close family member who can be trained, made accountable to look for side effects, aberrant behaviors and to monitor functional status, should be assigned to high-risk patients at the time of prescribing [10]. It is the system's and physician's responsibility to understand this aspect of patient care (drug-induced loss of well-balanced brain function) and serve to protect patients from self-harm. It is foremost in our code of ethics—to first do no harm.

If the above ethical statements are accepted as true; if proper judgment is accepted as being important for cognition and autonomy to exist; and if the brain disease model of dependence and addiction, the pain matrix, and the understanding that loss of behavioral control is a pharmacologic-induced phenomenon are also believed to be fact, then American laws governing this aspect of medical care are woefully inadequate and do not reflect the realities of our current understanding of the neuropsychopharmacology related to opioid use. The reality of the opioid epidemic is proof that a cultural tragedy is unfolding. A legal consideration is to write laws that provide guidance: redefine capacity in the context of opioid use, assign a responsible party with the goal to protect the unconscious brain, and create system safeguards to protect ourselves from this human vulnerability.

Current laws reflect the notion that behavior is a result of free will, which is false and leads to a life of self-neglect, unemployment, high risk of overdose, chronic pain, recurrent hospitalizations, psychiatric disorders, malnutrition, loss of barriers of infection, overutilization, homelessness, joblessness, violence, despair, and early death. The structures that govern us must be changed to reflect the reality that the human brain is not an organ that evolved to be an independent entity only concerned with self-preservation, but rather it adapted over 1.2 million years among other primates in community. The human brain is arguably the most important organizational structure on Earth, and it is interconnected by the subconscious mind to other human beings to form a powerful network. It is only prudent that we, as a nation, do everything humanly possible to protect this vital network so that it reflects a perceived reality based not on deception but rather on a reality that is true to the natural world.

Hyperalgesia, Chronic Pain, and Central Sensitization

True story: A 28-year-old female was transferred from an outside hospital for uncontrolled complications that were progressing after a small bowel resection. Three months earlier, she had been admitted with acute abdominal pain and found to have acute intestinal ischemia. A small bowel resection with ileostomy was done. Her postoperative course was complicated by progressive abdominal pain, inability to eat, severe protein malnutrition requiring total parenteral nutrition (TPN), upper extremity deep vein thrombosis, and pulmonary embolus. An ultrasound performed after admission revealed active thrombosis associated with a PICC line, and hematology was consulted for evaluation for a hypercoagulable state. The patient's pain story

included worsening pain that progressed after surgery despite escalation of opioid therapy. Abdominal pain was associated with uncontrolled nausea and vomiting, headaches, and increased anxiety and progressed to include severe pain associated with venipunctures for lab draws. Her previous physicians had told her that Dilaudid (hydromorphone) would take care of all of her painful conditions. She displayed high negative expressive emotions when attempts were made to do routine medical procedures, such as performing a pelvic and abdominal exam, placing an IV line, and obtaining labs. She cried and refused removal of the PICC line due to fear of the pain involved with its removal. Her mother tried to calm her down on the first hospital day, and the patient yelled in tears, "You do not know my pain!" Even placing the stethoscope upon her chest elicited a painful jerk response. At her hospital admission, opioids were stopped. She was placed on medication for central sensitization, given verbal reassurance for fear reduction, and started on a newer therapy for anticoagulation to minimize blood draws. She began eating, TPN was discontinued, the PICC line was removed, and she was discharged in 2 days with her pain well controlled.

Not all pain can be treated with opioids. The above patient had opioid-induced hyperalgesia. Providers frequently overlook this important cause of pain that is associated with fear and avoidance behavior and with pain catastrophizing. Opioid-induced hyperalgesia has been reported in the medical literature since 1870, is characterized as increased sensitization to painful stimuli after exposure to opioids, and often mimics the patient's original painful condition [8]. Opioid-induced hyperalgesia is postulated to have both a central and a spinal origin [8]. It is both a type of central sensitization caused by neuroinflammation in the midbrain structures and a defect of descending modulation in the spinal cord [8]. Opioids have been shown to disrupt the function of glial cells, whose job is to tone down the pain signal in the dorsal horn of the spinal cord [8]. Opioids are no longer effective and have become harmful, often perpetuating the painful condition. When patients fail to resolve their pain with opioids, opioid-induced hyperalgesia needs to be considered. A pain history, opioid history, and psychiatric history are critical to the formation of a treatment plan for a patient who has been formerly treated with opioids.

Chronic pain is defined as pain lasting more than 3 months. Chronic pain is not the same disease as acute pain. Chronic pain is associated with fear and avoidance behaviors, so attention needs to be paid to psychosocial issues. Chronic pain has a different pathophysiology than acute pain and requires a different treatment approach, a multimodal approach. Chronic pain can impact many body systems, including the gastrointestinal, psychological, endocrine, and sleep. Chronic pain implies that neuroinflammation and neuroplastic changes in the brain have begun to develop. Complicating matters, there is a frequent overlap of persistent pain after an acute illness with dependency and opioid use disorder. The pathophysiology of chronic pain can include central pain syndromes, central sensitization of the periaqueductal grey zone and rostral ventral medulla of the midbrain, or a failure of descending modulation of glial cells in the dorsal horn of the spinal cord (complex regional pain syndrome) or it can be peripheral in origin, such as peripheral neuropathy or osteoarthritis [8].

With central pain syndromes, the brain has constructed a painful reality within the unconscious brain structures. Common examples of central pain include

Table 13.6 Central pain syndromes

• Parkinson disease
• Multiple sclerosis
• Phantom limb pain
• Post-stroke pain
• SPINAL injury

phantom limb pain; post-stroke pain; and pain associated with Parkinson disease, spinal cord injury, and multiple sclerosis. A pain signature arises and persists from direct injury to nerve tissue. Microglial activation and neuroinflammation with the release of cytokines, interleukins, and glutamate cause cell death and lead to mental dysfunction and depression [9]. This is a type of central sensitization that originates in the brain. Opioids fail to relieve central pain and can potentiate the pain (Table 13.6).

In complex regional pain syndrome, which is a failure of descending modulation involving glial cell function in the dorsal horn of the spinal cord, the perception of pain is also real to the patient, and these cases also need a multimodal treatment approach [9]. The original source of the pain signature arises from a peripheral nerve and is augmented at the level of the spinal cord. These patients are difficult to treat and need referral to a chronic pain specialist.

Opioid withdrawal pain is also chronic, cyclical, associated with anxiety, and unrecognized. Pain frequently relapses as patients run out of their medications and present to the ED, clinic, or hospital for more tablets. Opioid withdrawal pain has a similar pathophysiology to opioid-induced hyperalgesia and should be considered when opioid therapy fails [8]. Because the perception of pain during withdrawal syndromes can be greater than the original painful event because of the pharmacologic effects of the opioid, opioid withdrawal should be undertaken in a supervised setting. Objective monitoring of the patient's functional status (not the subjective pain scale) helps to dictate the pace of the weaning process. For the patient to succeed with withdrawal, he/she will need reassurance and guidance through a transition period. Opioids induce fear and anxiety, and fear and anxiety increase pain perception, so patients can be very emotional and expressive when they present with withdrawal. The anxiety is usually temporary and can be managed with an explanation to help them obtain conscious control over their impulsive instincts. Patients can be taught that when opioids wear off, the midbrain structures release the pain signature and the pleasure signal in the nucleus accumbens also diminishes, enhancing pain perception. Patients respond well to dialog about the central origins of their pain and can gain understanding that their pain perception is real even though their physical condition is stable. A useful analogy that patients can understand is when one moves one's hand from a cold bath to a warm one, the temperature feels hot. Many patients are willing to undergo this transition, even if it requires some temporary suffering, if the goal is independence from pharmacotherapy and improved quality of life. Patients need verbal reassurance that their medical condition is stable during weaning, which is a sensitive transition period. Also, distraction is a known treatment method to assist in this endeavor (Table 13.7).

Opioids also turn off the natural endogenous opioid system in the brain, and it may take 3–5 days to resolve after the opioid is discontinued. The pain perception of central sensitization can take 1 month to resolve [9].

Table 13.7 Evidence of central sensitization

• Opioid withdrawal pain
• Hyperalgesia
• Allodynia—Opioid-induced increased pain sensitivity
• Migraine headache, analgesia-induced headache
• Fibromyalgia
• Opioids fail to bring relief

Table 13.8 Functional status

• Activities of daily living
• Instrumental activities of daily living
• Pain disability score
• AMPAC (activity measure for post acute care) scores
• Sleep performance
• Nutrition
• Albumin level
• Number of aberrant behaviors
• Compliance with other necessary care

In all of types of chronic pain, the provider must taper and discontinue opioids and use evidence-based pharmacotherapies and a multimodal integrative treatment approach with attention to psychosocial care. Functional status, instead of using the subjective pain scale, must be evaluated regularly to assess the need for ongoing medication and treatment. Functional status can be assessed by measuring activities of daily living, instrumental activities of daily living, pain disability scores, pain interference indices, AMPAC scores (Activity Measure for Post Acute Care), oral intake, sleep quality, number of aberrant behaviors, compliance with other necessary treatments, and more. Evidence-based treatment for chronic pain includes multidisciplinary techniques such as exercise, cognitive behavior therapy, mindfulness, stress reduction, physical therapy, psychotherapy, massage, group therapies, methods of distraction, and interventional procedures [10] (Table 13.8).

Primary care physicians and hospitalists need the guidance and experience of a good chronic pain and addiction expert close at hand, or they must be allotted the time needed to address the patient's complicated psychosocial issues and other pain-related behaviors. Advanced practice practitioners or nurse pain educators could be trained and are well suited to perform in this role with the guidance and support of a pain management physician, internist, and/or psychiatrist. Because chronic pain, opioid dependence, and psychiatric illness often occur together, this expert must be skilled in all three conditions. The expert and the provider both need alternative remedies for the treatment of chronic pain readily available—remedies that reduce fear and focus on the social and psychological aspects of the pain syndrome. Providers need to recognize the psychological aspects of this disease that include fear and avoidance

Table 13.9 Nonpharmacologic treatment for central sensitization (brain pain)

• Conscious mind
– Education, cognitive behavior therapies, acceptance therapies
– Teach how to recognize and avoid unconscious impulses
– Teach coping skills (serial relaxation, deep breathing, etc.)
– Teach to recognize fear and avoidance behaviors (catastrophizing)
• Unconscious mind
– Distraction
– Biopsychosocial approach
– Functional rehabilitation

behaviors, negative emotions, and catastrophizing thoughts in order to steer patients toward acceptance and commitment to self-care and the avoidance of unnecessary and potentially harmful procedures or drugs. Functional restoration programs can benefit patients with both chronic pain and opioid dependence (Table 13.9).

Addiction

True story: A 24-year-old male was admitted to the hospital with tricuspid valve endocarditis, septic pulmonary emboli, and active heroin abuse. He was witnessed on hospital camera selling oxycodone to another patient in the hospital. Security was consulted, the two patients were separated, and the patient expressed that he wanted treatment for his addiction and infection. Case managers were not able to place him in a skilled unit due to behavior disturbances and previous known behavior history. Addiction psychiatry was consulted, and the patient was started on Suboxone (buprenorphine and naloxone) therapy in the hospital setting. His behavior came under control. He completed antibiotic therapy. There was no further illegal activity or disruptive behavior, and he was discharged with proper follow-up for his addiction. Later, during the hospital stay, the patient admitted to severe childhood traumas, including the murder of his father and lack of attachment to a psychologically ill mother.

The above case demonstrates how proper treatment of addiction in the hospital setting can improve efficiency of care, eliminating costly disruptive behaviors, readmissions, and morbidity. Addiction affects everyone, especially family members over multiple generations and nursing staff who must care for the patient in the hospital setting. Managing the patient with the goal to control his behavior is paramount to the success of other medical care. Healthcare systems must recognize and embrace this change for greater efficiency of delivery of other healthcare services.

This is also a safety concern as heroin addicts are known for their criminal activity and increased risk of death by gunfire.

Addiction can be a pure physical dependency if exposure is long enough, but most addiction is a disease of human intimacy [11]. It is a set of adaptive, learned responses to early-life dysfunction. Addicts learn early in life through abuse, neglect, and trauma that turning to other people for support and validation leaves them feeling worse than before they reached out. When addicts face challenges and stress, they automatically, without conscious thought, turn to an addictive substance rather than seek support through emotional connection [11]. Addictions are adaptive coping responses to complex childhood trauma and related attachment disorders [11]. Addicts fear and avoid emotional intimacy. Opioid dependence without a history of psychological factors is readily reversible if recognized. When there is a psychological factor, relapse is much higher [11]. Any pleasurable substance or distracting activity can become an addiction. Also, early exposure to a substance or behavior is a common environmental risk factor [11]. Age of first use should be documented and taken into consideration during pain management assessments prior to procedures.

Attachment theory is a psychological theoretical construct developed in the 1940s–1950s, during research conducted on orphaned children after World War II. Infants, war widows, juvenile delinquents, married couples, and monkeys who did not feel emotionally attached in childhood suffered depression, anxiety, and self-destruction later in life. Today, it is widely accepted that early-life family dysfunction leads to later-life emotional and psychological disorders. These children have a lifelong battle with shame, feel unworthy of love, and avoid emotional vulnerability. They grow up to suffer shame, anxiety, anger, and fear and are not able to trust others to alleviate their emotional discomfort in a healthy manner. They find a maladaptive coping mechanism with addictive substances or behaviors, which is the easiest way to not feel the pain of their emotional disconnection [11]. As the pharmacologic effect of the substance escalates with anatomic and functional neuroplastic changes in brain circuits, they become even more emotionally disconnected. When addiction is viewed as an intimacy disorder, treatment is not only sobriety but also a human connection with a safe, supportive, and empathetic other [11].

There is a dearth of addiction services nationwide. Outpatient and inpatient services are needed. Treatment programs need to be focused on cessation of the offending substance and the development of reliable healthy emotional bonds rather than focusing on will power and the fear of future consequences [11]. To connect and reintegrate these patients back into the community, individualized addiction treatment including cessation and withdrawal should be followed by group therapy and then with subsidized jobs and social programs. Addicts need to learn to how to interact on an emotionally intimate level with other recovering addicts and then with other people that they can learn to trust while they integrate back into self-management of their physical and psychological conditions.

Key Points

1. The cardinal features of the opioid epidemic include diversion of tablets, chronic pain, addiction, psychiatric illness, and overutilization of healthcare resources.
2. Chronic pain, opioid dependence and related psychiatric disorders should be considered to be a single disease that deserves comprehensive chronic disease management strategy.
3. Opioids directly affect subconscious brain structures including the prefrontal cortex, nucleus accumbens, ventral tegmental area, amygdala, rostral ventral medulla, and periaqueductal grey zone.
4. The brain disease model of dependence and addiction is fully established in science and demonstrates how adaptive changes that occur early in the disease progression promote behaviors toward addiction but can resolve with abstinence, and later in the disease, habit circuitry is established and permanent.
5. Opioids work by altering transmission of the pain signature through the periaqueductal grey zone and rostral ventral medulla. They also cause neuroinflammation and central sensitization, and reinforce the memory of the pain signature.

References

1. Meyer R, Patel AM, Rattana SK, Quock TP, Mody SH. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul Health Manag. 2014;17(6):372–87. doi:10.1089/pop.2013.0098.
2. Martin L, Laderman M, Hyatt J, Krueger J. Addressing the opioid crisis in the United States. IHI Innovation Report. Cambridge, MA: Institute for Healthcare Improvement; 2016. http://www.ihi.org/resources/Pages/Publications/Addressing-Opioid-Crisis-US.aspx?utm_campaign=tw&utm_source=hs_email&utm_medium=email&utm_content=32920825&_hsenc=p2ANqtz-_8KaK1j-okcapyVh9HSIFKr8A4kaadvwpmLjK9McIUktS_NFXhq8GrP7FdlQ94rJ6GtQhwAufw6H1N_O3H2TjdcBz4zA&_hsmi=32920016. Accessed 9 Dec 2016.
3. A brief history of opioids: pain, opioids, and medicinal use. The Atlantic. Purdue Health. http://www.theatlantic.com/sponsored/purdue-health/a-brief-history-of-opioids/184/. Accessed 28 Sept 2016.
4. Mlodinow L. Subliminal: how your unconscious mind rules your behavior. New York, NY: Vintage Books; 2012.
5. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology. 2008;33(1):166–80.
6. Hooten WM. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. Mayo Clin Proc. 2016;91(7):955–70. doi:10.1016/j.mayocp.2016.04.029.
7. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. N Engl J Med. 2016;374(4):363–71. doi:10.1056/NEJMra1511480.
8. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145–61.
9. Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: epidemiology, etiology, and treatment options. Arch Neurol. 2001;58(10):1547–50.
10. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65(1):1–49. doi:10.15585/mmwr.rr6501e1.
11. Weiss R. Why do people with addictions seek to escape rather than connect? A look at the approach to addiction treatment. Consultant. 2016;56(9):786–90.

Suggested Learning

1. TED: The Hardest Pill to Swallow. http://www.youtube.com/watch?v=tlec4V8p6y4&sns=em.
2. TED: Why Things Hurt. http://www.youtube.com/watch?v=gwd-wLdIHjs&sns=em.
3. TED: Pain, Is it All in Your Mind? http://www.youtube.com/watch?v=tiwmVTScusg&sns=em.s.

Chapter 14
Solving America's Prescription Epidemic: Solutions, Current Practices, Provider Internal Skills, and Systems Approach to Care

Marianne Maumus

Prevention of Opioid Dependence and Chronic Pain

The Institute for Healthcare Improvement outlined seven operating principles to address the prescription opioid crisis [1]:

1. Patients need appropriate pain management.
2. Science and clinical knowledge about how opioids work have evolved, so policies and practices must also evolve.
3. The latest evidence about appropriate use and risks of opioids for both acute and chronic pain needs to be disseminated to providers and integrated into routine care.
4. Different provider types have varying degrees of training on pain management, so provider education must take these differences into account.
5. Patients need to be better informed about the effectiveness and risks of opioids.
6. Use of prescription opioids is linked to heroin and needs to be recognized as such.
7. Any intervention effort needs to take into account possible unintended consequences for other parts of the system.

Each of these principles identifies an obstacle that interferes with the prevention of this disease.

The key to success for patients who must take opioids is prevention of opioid dependence. Phenotypic neuroplastic changes have been detected microscopically to begin as early as 5 weeks into therapy [2]. Action should be taken early to guide patients into nonpharmacological care and other treatments before aberrant symptoms develop that are indicative of damage to unconscious brain structures. Patients

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should be weaned from opioids as soon as possible before the transition to chronic pain and opioid dependence is suspected. Healthcare systems need to provide adequate safeguards and structures to prevent dependence and opioid use disorder because many times the cause of opioid dependence is iatrogenic. These safeguards could be established by making changes to the electronic medical record (EMR) that improve provider communication between different clinical settings and among various hospitals, forming chronic pain clinics and functional restoration programs, and supporting public education programs that discuss risks and pathophysiology. Patients need to be informed at the onset of prescribing of all the risks, including damage to the unconscious brain, opioid dependence, loss of autonomy, risk of treatment failure, risk of withdrawal, and risk of opioid use disorder. Patients should be taught the brain disease model of dependence and addiction before a prescription is written. Patients with dependence and opioid use disorder have the right to a proper diagnosis and treatment. Hospital systems and governments have a responsibility to appropriately label patients in order to protect them and to steer them into proper care.

Alternative treatments for pain should be first line. According to the National Safety Council, the efficacy of nonopioid pharmacotherapies has been shown to be greater than that of morphine [3]. The Cochrane Collaboration reviewed treatment of postoperative acute pain and found that combining ibuprofen 200 mg with acetaminophen 500 mg outperformed both oxycodone 15 mg and oxycodone 10 mg + acetaminophen 650 mg [3]. Bandolier, an independent organization in Europe that reports on evidence-based methods, produced a table comparing the efficacy of oral and injectable medications for pain. Diclofenac 100 mg, celecoxib 400 mg, and ibuprofen 400 mg outperformed morphine 10 mg IM, oxycodone 5 mg + acetaminophen 325 mg, and tramadol 50 mg [3]. Furthermore, the National Safety Council reported that no evidence supports the idea that opioids are helpful in chronic pain [3]. Epidemiology studies also fail to confirm the efficacy of opioid therapy for chronic non-cancer pain [3]. A large study in Denmark revealed that patients treated with long-term opioids (>4 months) had higher levels of pain, had a poorer quality of life, and were less functional than those who were not on chronic opioid therapy [3].

In pediatric patients, Miech et al. demonstrated in 2015 that legitimate use of opioids before the 12th grade is independently associated with future opioid misuse among patients who have little drug experience and who disapprove of illegal drug use [4]. These results suggest an unrecognized risk of opioid prescribing. Other studies have also associated short-term prescriptions with misuse in youth. When prescribing opioids, the group of concern is adolescents without a history of illegal drug use. History of little or no use of marijuana may be the indicator that can identify this high-risk group [4]. Adolescents are known to be vulnerable to illicit and prescription drug abuse due to the underdevelopment of the subconscious brain structures that do not mature until age 24. Exposure is theorized to permanently change neural circuits, impair cognitive function and development, and increase the risk of future psychological illness.

Distraction is a well-known pain reliever [5]. New modalities such as virtual reality (VR) are presently being studied and used in burn units and for cancer procedures, wound care in veterans, routine medical procedures, and chronic pain such as neck and back pain. It is postulated that VR acts as a nonpharmacologic form of analgesia by exerting an array of emotional affective, emotion-based cognitive and attentional processes on the brain's pain matrix. It is theorized that human

beings have a limited capacity of attention, and an individual must attend to a painful stimulus for it to be perceived. Also, sensory distractions delivered by VR technology can remove the sensory systems (visual, auditory, touch) from the perception formation and interfere with intercortical modulation among signaling pathways within the pain matrix [5]. Distraction can also be a useful approach in the hospital setting. Pediatric nurses have used distraction techniques to place IV lines in small children for years [5]. Physical therapy, nursing, house staff, pastoral care, hospital volunteers, alternative treatments such as pet therapy, music therapy, and more serve to remove the patient from reminders of the pain stimulus and alleviate negative cognitions. Green infrastructure and useful distractions built into the physical plant can encourage walking, mobility, and social interactions.

Current Practice Management

True story: A 43-year-old female was admitted for a pneumothorax related to sarcoidosis. It was difficult to manage, resulting in a prolonged ICU stay and 6 chest tubes over 2 months. After removal of the last chest tube, the patient was transferred to the hospital medicine service. Her IV pain medicine was converted to oral therapy, but the oral morphine equivalent (OME) dose was increased to ensure analgesia. The patient expressed anxiety related to the change. She required a stay in a skilled nursing unit for deconditioning and was maintained on long-acting opioid therapy. She was discharged and sent to a new primary care physician who immediately became alarmed at the high opioid dose and initiated a pain contract and a plan for gradual withdrawal. The dose was lowered in a stepwise fashion. The patient then switched primary care doctors. The second primary care doctor maintained and refilled her opioid prescription without initiating a contract.

One year later, the patient was admitted for nausea and vomiting and was found to have opioid withdrawal due to running out of tablets ahead of schedule. She was placed on IV Dilaudid (hydromorphone) and her symptoms immediately improved. The following morning, she was reluctant to change to oral medication, threatened to call patient relations, and directed aggressive verbal remarks at the resident physicians. The medical team changed staff physicians the next day, and the second staff physician called for a multidisciplinary team including nursing, therapy, all physicians involved in her care, and administrators from patient relations. The patient's primary care physician was updated by phone. When staff entered her room, it was apparent that the patient was very anxious. The staff physician addressed her fear with the first sentence by stating, "I just looked at all of your x-rays, and the pneumothorax is gone. It has been over a year and has not come back. You are stable." The patient immediately felt better and then asked, "Then why do I still feel pain?" This opened a friendly conversation about the pharmacology of opioids, including long-term late effects. Written patient education materials were given to her, and she was directed to pertinent websites. Recommendations for withdrawal were made, but if she was unable to finish withdrawing in the hospital, medication-assisted treatment with Suboxone (buprenorphine and naloxone) was recommended. The patient decided to stop opioid therapy and was discharged 2 days later.

The above case demonstrates how proper use of opioids can easily go wayward in a fractionated healthcare system. Inability of providers to recognize fear and avoidance behaviors due to lack of training and experience, lack of communication between serial providers in different clinical settings, system pressures that reduce a provider's time to address the patient's psychosocial needs, and pharmacologically induced drug-seeking behavior by the patient all contributed to this patient's progressive opioid dependency. Treatment with opioids is appropriate for postsurgical pain and end-of-life care, but prevention of opioid dependence and opioid use disorder needs to be a priority when treating young, highly functional patients after a routine illness. All providers who prescribe opioids must have the basic skills to recognize fear and avoidance behaviors and have time allotted to address them with the patient. These providers need standardized methods to monitor tablets, initiate pain contracts, and measure the patient's functional status with the goal to reduce overprescribing. All providers who start opioid therapy need to be responsible for stopping it. A systematic procedure for stopping opioid therapy needs to be adopted nationwide. Ideally, there would be tools built into the healthcare system to rescue this patient and trigger the provider to look at the big picture in order to steer patients such as this into the right treatment protocol for chronic pain. These tools include changes to the EMR for the purpose of improving communication; alerting the provider to the patient's opioid, pain, and psychiatric histories; adopting standardized accepted average time frames for certain procedures with stop dates planned for the treatment of painful procedures; accessing professionals who specialize in chronic pain; and recommending functional restoration programs for patients who have difficulty reintegrating back into society after an illness.

In the 1980s, perceived undertreatment of pain led to the development of pain advocacy groups who wrote guidelines that were not developed from evidence-based medicine [6]. Physicians were not adequately trained in pain management [6]. Physicians still appear to provide prescriptions for opioids without appropriate training, and this practice contributes to doctor shopping [6]. Because prescribing behavior is variable among physicians, opioid-dependent patients quickly learn to seek out liberal prescribers. Many pain advocacy groups were also supported financially by the pharmaceutical industry and held education conferences to instruct primary care physicians who treat 20- to 30-year-olds. They frequently omitted the brain disease model of dependence and addiction in their coursework and relied on teaching from a palliative care/end-of-life perspective. Today's primary care physician less frequently treats end-of-life patients in the hospice setting and needs instruction to assist in caring for patients with chronic pain, opioid dependency, and opioid use disorder.

Overprescribing during the last 20 years has led to widespread diversion of tablets in the community, creating opportunities for exposure and imperceptible changes of brain function in new individuals. New patients with chronic pain, opioid dependence, and psychiatric disorders drive overutilization. This epidemic is a nationwide cultural pathology that is a direct result of withdrawing from evidenced-based medicine, undereducating physicians, and undersupporting the treatment of patients with chronic pain and psychiatric disorders. Our new goal as a healthcare system is to reverse the process by providing evidence-based treatments for both chronic pain and addiction and to move patients back toward self-management and independence (Fig. 14.1).

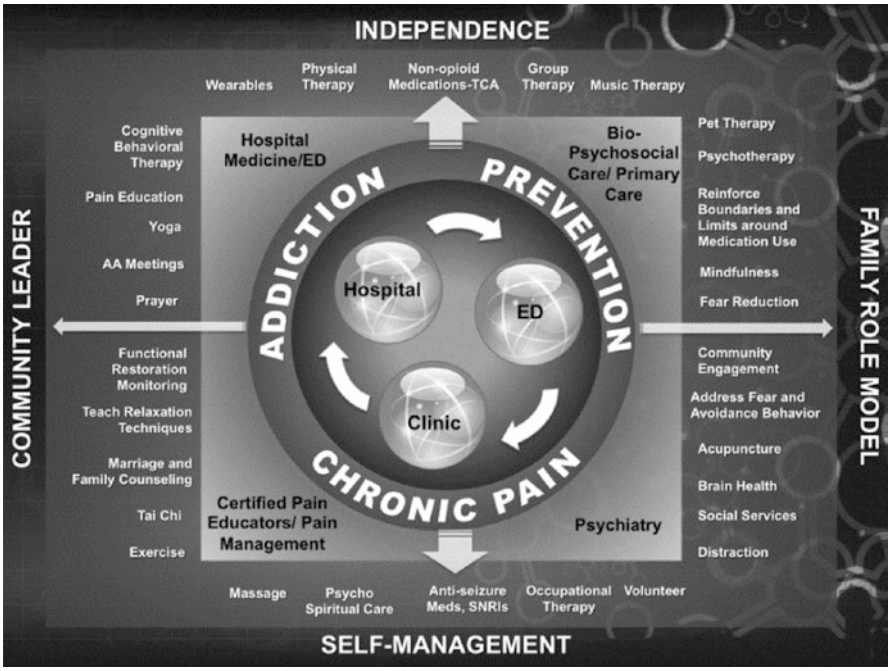

Fig. 14.1 Movement of patients from the hospital system toward independence and self-management with evidence based medicine for chronic pain and addiction [1, 3, 6–14]

The Institute for Healthcare Improvement identifies four primary populations that are affected by opioid use: the naïve patient, the high-dose chronic user, the opioid dependent seeking within the healthcare system, and the opioid dependent seeking outside of healthcare [1]. Prevention can eliminate opportunities for opioid exposure, but when acute pain transitions to chronic pain, evidence-based methods are needed to intercede, and the patient should be referred for functional restoration, which encompasses a multimodal approach to chronic pain treatment, psychiatric care, and treatment for opioid dependence. Opioids need to be compassionately tapered with concomitant objective measures of functional status. Opioid-seeking behavior needs to be addressed with the goal of keeping the patient within the healthcare system to prevent the transition to illegal activity. Addicted patients with subconscious aberrant behaviors who cannot stop opioid therapy need referral for medication-assisted treatment, such as long-term Suboxone (buprenorphine and naloxone) maintenance programs for gradual withdrawal.

Presently, in 2016, patients who frequent the ED and hospital have cyclical opioid withdrawal; they are continuously running out of their tablets and looking for more. Some have side effects and late effects of opioids and require hospitalization. Many have central pain or central sensitization, which is a type of pain that opioids cannot fix, and some are looking for real treatment options for their peripheral pain, their back pain, or their neuropathic pain that has not been treated with evidence-based methods. Many have iatrogenic opioid dependence and progress to opioid use

disorder. Opioid-dependent patients are anxious, and they do not understand the pathophysiologic cause of their pain. Patients who take opioids are not able to discern when the risks of opioid therapy begin to outweigh the benefits. In other words, patients cannot perceive when the therapeutic effect of the drug has passed and when dependency begins. The irrational unconscious brain takes over the patient's decision-making, and pain catastrophizing thoughts—the direct effect of the opioid—are observed clinically. The physician's job is to make the distinction between efficacy and dependence, address the patient's fear, keep the patient in a safe environment, and point out when opioids are no longer working and a different treatment approach is needed. This is a skill that must be taught and practiced, and it must be system supported. Without a healthcare system designed to prevent and treat chronic pain and opioid dependence, patients frequently fail to recover from their illness, fail to achieve academically in school, and lose their jobs and their insurance coverage.

Provider Internal Skills

Providers need certain clinical awareness and internal skills to address this patient group. When pathology of the unconscious brain structures is evidenced by the presence of aberrant behaviors, often the transition to opioid dependency is already present, and the patient's autonomy has been affected and lost. Aberrant behaviors need to be assessed in the appropriate context. The physician or provider must be confident in making clinical observations of unconscious aberrant behaviors and properly documenting them in the EMR.

Aberrant behaviors

• Manipulative behavior observed	• Multiple pharmacies
• Unwillingness to cooperate with assessment	• Self-inflicted wounds
• Untruthfulness directly observed	• Actions and behavior do not match patient's description of the pain
• Splitting healthcare providers	• Source of pain changes
• History of stolen or lost prescriptions	• Making false statements
• Reluctance to wean from/discontinue narcotic once acute illness is resolved	• Exaggeration of facts
• History of altering a prescription	• Recurrent admissions
• Doctor shopping or multiple doctors	• Reluctant to appropriately self-care (i.e., would care) or follow directions to prevent deterioration of the problem
• Hospital shopping or multiple hospitals	
• Multiple allergies	
• Request for specific therapy	
• Request for antihistamines with narcotic	

When faced with highly emotional patients in pain, physicians and providers must recognize their own empathy, replace it with compassion, and be able to purposefully detach emotionally from the patient in order to see the big picture and help the patient to see it as well. Empathy occurs when a person psychologically identifies with and experiences the feelings, thoughts, or attitudes of another. Compassion is the desire to help someone in need. With practice, physicians and providers can help patients recognize their irrational fears and gain conscious control of their behavior. This is often a difficult undertaking for the primary care physician who may have a long-term relationship with the patient. When providers care for patients in pain, they also experience unconscious psychological pain. System recognition of this fact is needed to properly manage patients with chronic pain and opioid dependence. In some circumstances, it may take the professionalism of multiple providers who courageously teach, coax, encourage, manipulate, and steer the patient toward independence and self-management over a long period of time. The patient's fear must be addressed with each visit, because ignoring it worsens both anxiety and pain. Also, clinicians need to take responsibility for decisions about medication choices and apply common sense to relieve this burden from the patient and his family. With the help of a well-trained, self-disciplined, experienced, and compassionate physician or provider, opioid-dependent and addicted patients can be healed. Their pain and functional status can improve by reducing dosages and using alternative treatments [7].

System Approach to Care

Evidence has emerged revealing that high healthcare utilization is tied to America's prescription epidemic [8–12]. The most common comorbidities of patients who are the highest utilizers include chronic pain (83%) and mental health/substance abuse (96%), followed by hypertension (54%), sickle cell anemia (42%), and diabetes (42%) [8]. Patients who are the highest utilizers of healthcare are medically and psychosocially complex patients who have recurrent admissions to the hospital and the ED. They have diagnostic uncertainty associated with their symptoms and concomitant psychosocial and substance use disorders. Less than 1% of patients account for 21% of national healthcare spending, and hospital costs are the largest category of national healthcare expenditures [8].

Two articles from the *Journal of Hospital Medicine* in July 2015 address the care of these patients [8, 13]. The first revealed that developing individualized care plans can reduce healthcare utilization. Investigators at Duke University studied 24 such patients, developed care plans, and followed their course by measuring length of stay, readmissions, and number of ED visits over 6 and 12 months. By instituting a Complex Care Plan Committee, they reduced inpatient admissions by 56% for the first 6 months and by 50.5% for the 12 months after implementation. They also reduced 30-day readmissions by 51.5%. The second study from July 2015 looked at 87,688 national HMO enrollees and found that the patients with higher opioid doses (>100 OME) for greater than 3 months had a significantly increased risk for all-cause hospitalization and longer inpatient stays [13]. This information emphasizes

the link between inpatient and outpatient care and the need for nonpharmacologic approaches for the treatment of chronic pain [14].

Hospital systems have an incentive to recognize the relationship between chronic pain, psychiatric disorders, and addiction and provide effective treatments. Evidence-based methods for treatment are available and are presently underutilized. Systems can promote alternative methods of pain relief to reduce exposure to opioids. Administrators should work to reduce variability in prescribing habits among their staff. System changes include using the EMR to coordinate care and improve communication among providers; using patient registries to monitor progress, send out alerts and patient education materials, and provide lists and caution banners for various providers in different care settings; creating opioid risk tools that can be automatically setup in the EMR as a stop/pause/think measure and provide management guidance; and establishing presets to minimize the number of tablets prescribed, alert for proper Naloxone use, and apply other safeguards. Comprehensive functional restoration programs should be designed to care for all three groups: patients with chronic pain, patients with psychiatric disorders, and patients with opioid dependence. Less comprehensive services are already present within specific departments and outside of the healthcare system but are loosely organized. Indeed, many private-sector services that improve pain and address psychosocial needs of patients already exist throughout the community, such as exercise facilities, yoga studios, meditation classes, and prayer groups. They need to be coordinated in an organized fashion so that patients can connect to them. Also, some patients need to be bridged into community programs and job opportunities. Healthcare systems have a responsibility to develop close relationships with community organizations, government entities, school systems, and religious institutions to coordinate care and to develop and support low-cost counseling services, functional restoration programs, and other systems for emotional support. Governments and religious institutions also have a mission to connect their constituencies who can aid people with those who are in need of emotional support and to provide low-cost counseling, behavior therapies, and nonpharmacologic pain-relieving methods that benefit the population.

To resolve this crisis, a social approach to care must be conceptualized and incorporated into routine clinical practice. Market rationality and the corporate agenda that have infiltrated current practice during the past 20 years have brought many efficiencies to the practice of medicine but have not brought an improvement in reducing healthcare costs any significant amount nor have they curbed morbidity and mortality rates. Understandably, negative feedback loops develop in any system that contains competing interests and is designed not only to serve the population but also functions to provide for a stable and competitive workforce. Priority must be placed where it rightly belongs. Medical decisions must be rooted in the truth of the pathophysiology to maintain the just practice of medicine. Those who have interest in developing a well-functioning healthcare system must go back to basics: to admit that social and economic conditions affect health, that the health of the population is a matter of social concern, and that society should promote health

through both individual and social means [15]. The patient must remain the center of our attention and be the primary focus for all efforts if wellness is to be the primary goal.

America's prescription epidemic is a negative feedback loop within our healthcare system, one that needs immediate attention because it is counter to our collective healthcare mission and the values that we share and because of the tremendous burden, both physical and financial, that it places upon society. As providers, we can only do our part in our individual roles. The diagram below attempts to conceptualize a pathway of care based on the natural course of this disease. This pathway recognizes the transition stages toward addiction, emphasizes the importance of prevention, and provides for specific branches along the course of the disease where treatment protocols can be created and followed (Fig. 14.2).

Several institutions have already made significant inroads toward solving this crisis. Kaiser Permanente implemented a large-scale, systematic strategy in an integrated healthcare delivery system and achieved an 85% reduction in OxyContin (oxycodone) prescriptions, a 90% reduction in opioid/acetaminophen combination prescriptions with >200 tablets, a 26% reduction in >120 OME per day patients, and an 84% decrease in opioid + benzodiazepine + carisoprodol triad prescriptions. Group Health Cooperative Puget Sound (Washington) implemented chronic pain guidelines and achieved a 50% reduction of patients on high-dose opioids (>120 OME per day) and reduced the average daily dose by half. Group Health Cooperative increased care plans for patients on chronic opioid therapy from 3 to 96% in 1 year and increased urine drug screening from 15 to 65% in 1 year. CareOregon made

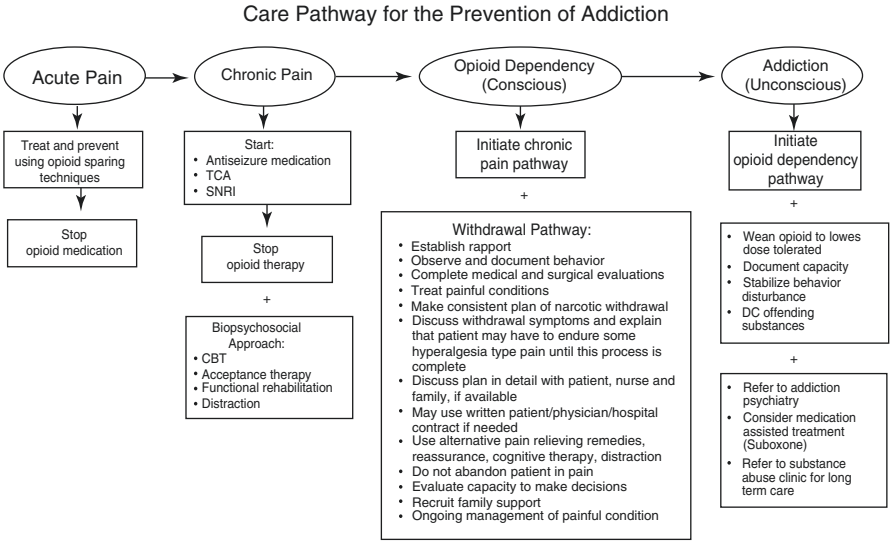

Fig. 14.2 Care pathway for the prevention of addiction [2, 16–19]

numerous system changes, including opening of a chronic pain clinic, and achieved a significant reduction in the number of patients on long-term chronic opioid therapy by more than 50% between 2011 and 2012 [1]. These successes illuminate the fact that solving America's prescription epidemic is achievable.

Provider Roles and Teamwork

This epidemic can only be solved with teamwork. The hospitalist will necessarily need to play a role in withdrawing patients from opioid therapy and in starting chronic pain regimens. Pain histories, opioid use histories, and psychiatric histories taken upon admission will clarify the patient's clinical condition, reasons for readmission, and the breakdown of the patient's psychosocial support system. Patients who have opioid complications, who fail opioid therapy, or have evidence of misuse should have their opioid use discontinued [7, 20]. For complex patients, a multidisciplinary team may need to be assembled, including the patient's nurse, therapists, pain management physician, primary care physician, psychiatrist, and representatives from patient relations, hospital management, and security. Functional status should be measured objectively daily, and aberrant behaviors should be documented by all providers to assess progress. Decisions can be made together and in the presence of the patient to prevent provider splitting and to develop a long-term care plan that can be flagged in the EMR. In the long-term care plan, direction can be suggested for the ED provider, the physical medicine and rehabilitation (PM&R) provider, and the primary care provider. Referrals to alternative pain and addiction services can be made and documented. In this way, the patient can be steered into the appropriate level of care by multiple providers as he/she relapses or seeks outlets for his/her addiction.

Primary care physicians will play a significant role in prevention, help the patient seek alternatives for pain relief, address psychosocial factors, and steer the patient to functional restoration programs. Primary care physicians, in a collaborative communitywide approach, have an important role in limiting the supply of opioids, raising awareness of the risk of opioid addiction, identifying and managing opioid-dependent populations, and treating opioid-addicted individuals [1]. They have the responsibility to check the prescription monitoring program and urine drug screen for all patients who take opioids and to screen all patients who have recently undergone withdrawal for relapse or substance use disorder. Standardized clinical guidelines, including the use of contracts and the writing of long-term care plans, need to be developed and followed by the entire primary care physician group to reduce variability so that patients learn to adhere to strict rules regarding the management of controlled substances and to screen for transitions to opioid dependence and substance use disorder.

Psychiatrists need to properly diagnose patients with opioid-related personality disorders and other mental illnesses. Proper diagnosis is paramount because

other providers need this information to make wise patient care decisions. This information needs to be easily found in the EMR even though it may be sensitive. Psychiatrists need to assess the risk of opioid therapy with standardized screening tools, document their findings in the EMR in a centralized location, and recommend alternative therapy. Suboxone (buprenorphine and naloxone) maintenance programs and cognitive behavioral therapies need to be expanded in both the inpatient and outpatient settings. If done correctly, medication-assisted treatment can improve efficiency and reduce disruptive behaviors in the inpatient and outpatient settings and promote gradual withdrawal and reduction of total daily OME dose. Healthcare systems need to expand psychiatry services in general. In the hospital, the psychiatrist needs to work with the hospitalist on multidisciplinary teams and help guide physician education about addiction in real time on hospital wards.

Pain management physicians need to take the hospital system lead, especially with provider and administrator education, in proper chronic pain management, including pharmacologic and nonpharmacologic treatment. They need to assist primary care physicians and expand chronic pain services in general, overseeing a team of nurse pain educators. They need to work with PM&R physicians and psychiatrists to design evidenced-based, pain-relieving functional restoration programs. Pain management physicians are experts on alternative remedies for pain, including pain-relieving procedures and the use of spinal stimulators. Specialty expertise is needed for recalcitrant cases and for complex regional pain syndrome. Alternative therapies for pain relief, such as IV lidocaine, inhaled nitrous oxide, IV propofol, IV ketamine, IV acetaminophen, and liposomal bupivacaine injections need to be expanded and made readily available in the hospital setting.

Physicians in the ED play a role in treating overdose, need to communicate with outside providers about complications, and need to reduce the number of tablets prescribed in the acute setting. Accurate diagnosis for pain treatment complications and for mental illness will place the patient in the appropriate treatment plan. There is no role for the treatment of chronic pain with opioids in the ED. Patients need to be steered into the appropriate care for addiction services as well as for chronic pain.

Surgeons and subspecialists (including dentists) who treat pain need to seek alternatives for opioid therapy and reduce the use of opioids as much as possible, recognizing that patients who undergo procedures always need excellence in pain relief. They should work to reduce the number of excess tablets distributed into the population. They should not refill medications for chronic pain and refer patients back to the appropriate prescriber. Preoperative evaluations should include a pain history, opioid use history, and psychiatric history, as well as documentation of the opioid risk tool score and a proper risk/benefit analysis before the patient is exposed to opioid medication. It is understandable that opioid therapy cannot be avoided for some patients, but weaning and stopping opioid therapy are the responsibilities of the provider who initiates it and care is not complete if this task is left undone.

Community/National Strategies

The Institute for Healthcare Improvement identified several key components for implementing a communitywide strategy to address the opioid crisis [1]:

1. Retrain providers who have been given misinformation pertaining to opioids.
2. Consider all providers since opioids are prescribed by a wide array of providers.
3. Identify alternative treatment options for pain management.
4. Create a role for pharmacists to build strong learning and feedback loops between providers, patients, and pharmacists.
5. Engage in public messaging.
6. "Flood the Zone" to deploy multiple methods across a community.
7. Recognize geography to create partnerships.
8. Include law enforcement as full partners to stop the vicious cycle and shift to illegal activity which accompanies prescription opioid addiction.

Nationally, there is ongoing research for better treatment approaches to pain. Thus far, the United States Congress has allocated $400 million in funding to combat this epidemic. Large hospital systems need to be involved with their development in clinical trials. The Mental Health Parity and Addiction Equity Act (2008) and the Affordable Care Act (2010) provide payment models for patients with substance use disorders and have been shown to reduce ED visits and hospital stays in three states [21]. The Comprehensive Addiction and Recovery Act (2016) provides funding for addiction, expands Suboxone (buprenorphine and naloxone) use, improves the prescription monitoring program, expands treatment in jails, and strives to provide some criminal justice reforms and mental health legislation. In a 2014 review of the economic burden of prescription opioid abuse in the United States, the mean annual excess healthcare cost for opioid abusers on Medicaid was reported to be $5874–$15,183, while the monetary benefit to society for substance abuse treatment was $11,487 per year per patient [6]. Most of this benefit was due to the reduced cost of crime and increased employment earnings [6].

Conclusion

Despite all the biopsychosocial pathology, there is much hope for the treatment of patients with chronic pain and addiction. Hospital systems can shift from dangerous opioid therapy to more scientific pain management. Patients with chronic pain and opioid dependence, when treated properly with abstinence and emotional support, can restore the function of the learning reward system and pain matrix. Their sense of pleasure and pain can return to normal, even though enduring neuroplasticity in the prefrontal cortex and the presence of corresponding memory loops will always increase the risk of relapse. The EMR can be utilized to communicate among

providers, allowing for teamwork between specialties. This teamwork can lead to excellence of care that was not possible in the past. Providers can be taught how to identify the three transition stages toward dependence and addiction and how to measure functional status. There is a defined timeline toward addiction that can be monitored closely. All physicians and providers who learn to prescribe opioids can also learn how to stop them. Also, integrating primary care and specialty behavioral health can improve the management of opioid dependence and related psychiatric factors, as well as the treatment of many addiction-related medical conditions. System changes can help to identify high-risk patients, reduce overprescribing, and help monitor patients who require opioid therapy more effectively to stop diversion of tablets in the community. Alternative treatments for acute and chronic pain can be made available.

Dr. Vivek H. Murthy, United States Surgeon General, stated, "We have to stop treating addiction as a moral failing, and start seeing it for what it is: a chronic disease that must be treated with urgency and compassion." Administrators, physicians, and all providers need to step up to the plate in a team approach with coordination of care in various clinical settings, supported by healthcare system reforms, in a compassionate and merciful stance with our patients. Providers need to accept the anger and heat that will undoubtedly come from weaning dependent patients during the necessary transition period, monitor their patients' functional status as a determinant of medication need, and guide them appropriately to wellness.

Key Points

- The Institute for Healthcare Improvement outlined seven operating principles to address the prescription opioid crisis that identify obstacles that interfere with the prevention of this disease.
- Alternatives to opioids should be first line. According to the National Safety Council, the efficacy of nonopioid pharmacotherapies has been shown to be greater than that of morphine.
- The physician's job is to make the distinction between efficacy and dependence, address the patient's fear, keep the patient in a safe environment, and point out when opioids are no longer working and a different treatment approach is needed. This is a skill that must be taught and practiced, and it must be system supported.
- Providers need certain clinical awareness and internal skills to address this patient group. When faced with highly emotional patients in pain, physicians and providers must recognize their own empathy, replace it with compassion, and be able to purposefully detach emotionally from the patient in order to see the big picture and help the patient to see it as well.
- The care pathway for the prevention of addiction recognizes the transition stages toward addiction, emphasizes the importance of prevention, and provides for specific branches along the course of the disease where treatment protocols can be created and followed.

References

1. Martin L, Laderman M, Hyatt J, Krueger J. Addressing the opioid crisis in the United States. IHI Innovation Report. Cambridge, MA: Institute for Healthcare Improvement; 2016. http://www.ihi.org/resources/Pages/Publications/Addressing-Opioid-Crisis-US.aspx?utm_campaign=tw&utm_source=hs_email&utm_medium=email&utm_content=32920825&_hsenc=p2ANqtz-_8KaK1j-okcapyVh9HSIFKr8A4kaadvwpmLjK9McIUktS_NFXhq8GrP7FdlQ94rJ6GtQhwAufw6H1N_O3H2TjdcBz4zA&_hsmi=32920016. Accessed 9 Dec 2016
2. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology. 2008;33(1):166–80.
3. Teater D. Evidence for the efficacy of pain medications. National Safety Council. http://www.nsc.org/RxDrugOverdoseDocuments/Evidence-Efficacy-Pain-Medications.pdf. Accessed 12 Aug 2016.
4. Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K. Prescription opioids in adolescence and future opioid misuse. Pediatrics. 2015;136(5):e1169–77. doi:10.1542/peds.2015-1364.
5. Li A, Montaño Z, Chen VJ, Gold JI. Virtual reality and pain management: current trends and future directions. Pain Manag. 2011;1(2):147–57.
6. Meyer R, Patel AM, Rattana SK, Quock TP, Mody SH. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul Health Manag. 2014;17(6):372–87. doi:10.1089/pop.2013.0098.
7. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. MMWR Recomm Rep. 2016;65(1):1–49. doi:10.15585/mmwr.rr6501e1.
8. Mercer T, Bae J, Kipnes J, Velazquez M, Thomas S, Setji N. The highest utilizers of care: individualized care plans to coordinate care, improve healthcare service utilization, and reduce costs at an academic tertiary care center. J Hosp Med. 2015;10(7):419–24. doi:10.1002/jhm.2351.
9. Mosher HJ, Jiang L, Vaughan Sarrazin MS, Cram P, Kaboli PJ, Vander Weg MW. Prevalence and characteristics of hospitalized adults on chronic opioid therapy. J Hosp Med. 2014;9(2):82–7. doi:10.1002/jhm.2113.
10. Blyth FM, March LM, Brnabic AJ, Cousins MJ. Chronic pain and frequent use of health care. Pain. 2004;111(1–2):51–8.
11. Dart RC, Surratt HL, Cicero TJ, et al. Trends is opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015;372(3):241–8. doi:10.1056/NEJMsa1406143.
12. Dahms R, Hilger R, Quirk R. Use of restriction care plans to decrease medically unnecessary admissions and emergency department visits [abstract]. J Hosp Med. 2012;7(Suppl 2). http://www.shmabstracts.com/abstract/use-of-restriction-care-plans-to-decrease-medically-unnecessary-admissions-and-emergency-department-visits/. Accessed 3 Sept 2015.
13. Liang Y, Turner BJ. National cohort study of opioid analgesic dose and risk of future hospitalization. J Hosp Med. 2015;10(7):425–31. doi:10.1002/jhm.2350.
14. Anderson WG, Liao S, editors. Improving pain management for hospitalized medical patients: a society of hospital medicine implementation guide. Society of Hospital Medicine. http://tools.hospitalmedicine.org/resource_rooms/imp_guides/Pain_Management/PainMgmt_Final3.4.15.pdf. Accessed 20 Aug 2015.
15. Smith L, Anderson MR, Sidel VW. What is social medicine? Mon Rev. 2005;56(8). http://monthlyreview.org/2005/01/01/what-is-social-medicine/. Accessed 9 Dec 2016.
16. Hooten WM. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. Mayo Clin Proc. 2016;91(7):955–70. doi:10.1016/j.mayocp.2016.04.029.
17. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145–61.
18. Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: epidemiology, etiology, and treatment options. Arch Neurol. 2001;58(10):1547–50.
19. Weiss R. Why do people with addictions seek to escape rather than connect? A look at the approach to addiction treatment. Consultant. 2016;56(9):786–90.

20. MKSAP-16, Internal Medicine Section, page 36. Performance interpretation guidelines with norm tables. MKSAP 16. Medical Knowledge Self-Assessment Program. https://mksap.acponline.org/16/MKSAP_16_Performance_Interpretation_Guidelines_with_Norm_final.pdf. Accessed 9 Dec 2016.
21. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. N Engl J Med. 2016;374(4):363–71. doi:10.1056/NEJMra1511480.

Suggested Learning

1. TED: The Hardest Pill to Swallow. http://www.youtube.com/watch?v=tlec4V8p6y4&sns=em.
2. TED: Why Things Hurt. http://www.youtube.com/watch?v=gwd-wLdIHjs&sns=em.
3. TED: Pain, Is it All in Your Mind? http://www.youtube.com/watch?v=tiwmVTScusg&sns=em.

Chapter 15
The Opioid Risk Tool Assessing Opioid Risk: Why Is the Sensitive Question Important?

Marianne Maumus

Introduction

Assessing opioid risk is critical prior to prescribing if the goal is to prevent addiction. Included in the risk assessment should be the Opioid Risk Tool score, a pain history, an opioid history, a psychiatric history, a urine toxicology screen, calculation of the oral morphine equivalent dose, and a check of the Prescription Monitoring Program. The Opioid Risk Tool is a validated 5-item questionnaire that predicts future aberrant behaviors consistent with opioid dependency and addiction [1].

Providers sometimes feel discomfort addressing the sensitive questions about psychiatry history, especially about preadolescent sexual experience, but this discomfort is unfounded and based on gender-specific biases that must be addressed if any resolution to the opioid crisis in the United States is to be attained. Traditionally, the practice of medicine has been a male-dominated field that has sometimes failed to address the needs of women—both in clinical practice and in research [2]. Another facet of gender bias is reflected in the lack of incorporation of gender data into evidence-based medicine [3]. Healthcare systems must address gender biases structurally by applying evidence-based protocols to routine care. All physicians should be comfortable addressing the health risks of their patients as a matter of standard practice. If a provider is not comfortable assessing the risks of a certain treatment or medication, then he/she should not be providing that particular therapeutic option.

Although opioids have greatly enhanced pain management, opium has been used by humans since ancient times to control human behavior [4]. It is well known that opioids are used by criminals to enslave populations and to force girls into the sex trade and that opioids are used within families to alter behaviors and loyalties.

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Opioids affect judgment, memory formation, and emotional control by causing neuroplastic changes in the prefrontal lobe, the nucleus accumbens, the ventral tegmental area, the amygdala, the periaqueductal grey zone, and the rostral ventral medulla of the midbrain [5]. Addiction is a progression of brain pathology. It is a three-tiered process that progresses from intracellular changes within nerve cells, to alteration of anatomy and function of neural circuits, to the formation of habit circuitry and permanent drug-related memories [5].

In the past, assessment of risk for opioids was overlooked, and the result is a widespread epidemic of prescription opioid abuse, overdose deaths, and the related transition to heroin abuse and crime [6]. Individuals who overdose are more likely to be white, female, and middle-aged [6]. In 2013, 16,235 Americans died from prescription opioid abuse [7]. Deaths from prescription painkiller overdoses among women have increased more than 400% since 1999, compared to 265% among men [8]. For every woman who dies of a prescription painkiller overdose, 30 present to the emergency department (ED) for painkiller misuse or abuse [8]. Nearly 48,000 women died of prescription painkiller overdoses between 1999 and 2010 [8]. Opioid prescription medication affects women in different ways than men. Women are more likely to have chronic pain, are more likely to be prescribed painkillers, and are given higher doses for longer periods of time than men [8]. Women become dependent more quickly than men [8]. Women are more likely to engage in doctor shopping than men [8]. Abuse of prescription pain medication by pregnant women puts their infants at risk. Neonatal abstinence syndrome grew by 300% in the United States between 2000 and 2009 [8]. Prescription pain medications are involved in 1 in 10 suicides among women [6]. The opioid epidemic is not strictly a women's problem, but these numbers and facts underscore the reality that gender plays an important role in the prescribing and in outcomes related to the use of these dangerous medications.

Addiction and Women's Health

Addiction is a disorder of human intimacy [9], a set of learned responses to early-life dysfunction. Addictions are adaptive coping responses to complex childhood trauma and related attachment disorders [9]. Opioid dependence without a history of psychological factors is readily reversible if recognized [9]. When a psychological factor is present, the rate of relapse is much higher [9].

Child sexual abuse has been linked to a lack of self-protection in adults and is a risk factor for the initiation and escalation of substance use among women [10]. The attachment disorder resulting from child neglect and child sexual abuse causes the patient to turn to an addictive substance rather than to seek support through an emotional connection when he/she is faced with a significant challenge or stress [7]. Large numbers of women who seek treatment for substance use disorders report sexual and/or physical abuse in childhood [10]. Childhood sexual abuse promotes promiscuous and/or unprotected sex and intravenous drug abuse, and both are associated with increasing rates of HIV and AIDS among women [10].

The American Congress of Obstetrics and Gynecology (ACOG) reports that 12–40% of children in the United States experience some sort of sexual abuse [11]. These patients come from all cultural, racial, and economic groups. Incest occurs with alarming frequency. Approximately one in five women has experienced child sexual abuse. Shame and stigma prevent survivors from disclosing abuse. Recognizing the extent of family violence, the ACOG strongly recommends that all women be screened for a history of sexual abuse. Patients overwhelmingly favor universal inquiry about sexual assault because they report a reluctance to initiate a discussion of the subject. Not asking about sexual abuse may give tacit support to the survivor's belief that abuse does not matter or does not have medical relevance [11]. Prescribing opioids to a patient with an unknown history of child abuse places that patient at risk for a lifetime of addiction. This fact underscores the importance of conducting this important screening before writing a prescription. Preadolescent sexual abuse and domestic violence questions are routine in pediatrics, obstetrics and gynecology, and ED medicine and should be routine to any provider who prescribes opioids.

Opioid Risk Tool: Evidenced-Based

The healthcare system cannot prevent addiction and all the associated poor medical and social outcomes of opioid dependency if a proper risk-benefit analysis is omitted. Healthcare providers need to recognize men and women who are at risk of prescription misuse and overdose and follow guidelines for responsible screening, prescribing, and monitoring [6]. Opioid risk assessments should be done prior to prescribing, before surgery, and during ongoing treatment of painful conditions.

Validated evidence-based tools must be used to assess the patient's risk before prescribing and should be incorporated into routine care and into the healthcare structure. Although risk assessment may be a change of practice for some providers, the need for risk assessment is also a cultural change that reflects the growing concern for women's health and children's health throughout our country. The healthcare system must be protective and open to communication about sensitive issues that some patients may have difficulty raising on their own. Other patients will soon get used to such routine care and will participate when they understand that the changes have been made for the greater good.

The Opioid Risk Tool is a validated evidence-based tool that provides a sensitive way to convey psychiatry history with a number score that supports patient privacy. It does not convey all risk and can miss some patients who are at high risk for adverse events. A score of 4–7 is moderate risk. A score >8 is high risk. The score is based on responses to questions about personal history of substance use, family history of substance use, history of psychological disease, age, and history of preadolescent sexual abuse [1]. Once these responses are obtained, they remain part of the patient's history and risk assessment, regardless of the age of the patient. Therefore, a provider does not need to repeat the questions every time a prescription is needed.

The Opioid Risk Tool can be used in the electronic medical record (EMR) to convey risk before prescribing (see Fig. 15.1). The number score can appear above

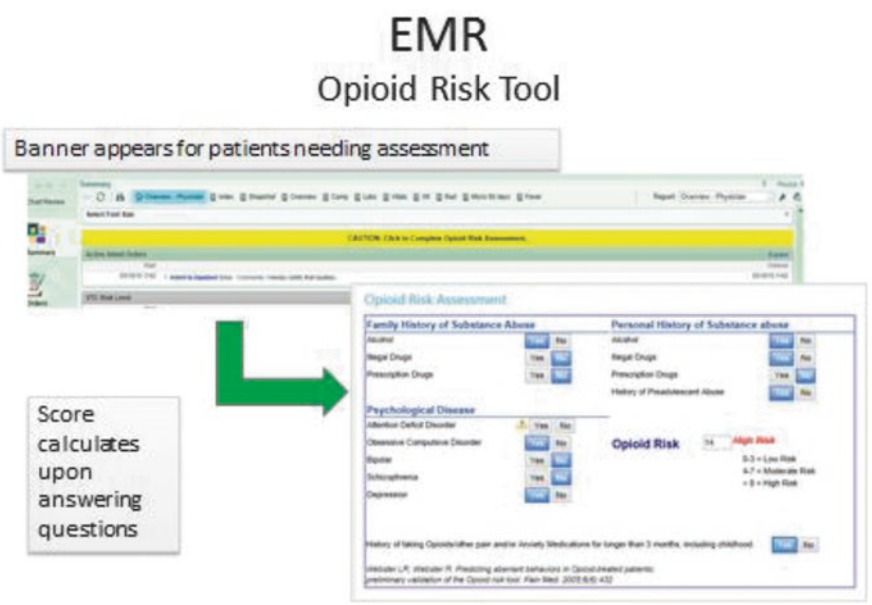

Fig. 15.1 An example of the opioid risk tool setup in the electronic medical record

the name of the opioid in the medication menu. In this way, the Opioid Risk Tool score becomes a stop/pause/think measure that alerts the provider to determine if a full risk-benefit analysis needs to be performed. The score should be a permanent aspect of the patient's EMR. Because the score has been determined by a previous provider, it can communicate risk in a sensitive fashion from visit to visit, from outpatient setting to inpatient setting, from previous physician to present physician, from a psychiatrist to the ED physician or hospitalist, and vice versa. If the score is moderate or high, the provider needs to take caution with prescribing, complete a thorough evaluation of risk, and make sure the appropriate outpatient follow-up is arranged. Alternatives to opioids; close follow-up with appropriate providers; attention to psychosocial factors; and quick referral to a functional restoration program or a pain rehabilitation center that offers physical therapy services, alternative remedies for pain, and cognitive behavior therapy should be considered before chronic pain or opioid dependency develop.

It is a minimum standard of care that the risk of addiction should be assessed prior to giving opioids to a patient. The Opioid Risk Tool meets that minimum standard. Recording the Opioid Risk Tool score in the EMR protects the patient from haphazard overprescribing and protects the provider from failing to perform an assessment. To ease the burden on providers, the EMR produces an Opioid Risk Tool form that should be completed upon writing of the first opioid prescription. The EMR can prefill certain parts of the form, including the question about preadolescent sexual abuse. Once the form is in the EMR, it will not need to be completed again except for adolescents who are at high risk and may have changing

histories. For adults, the provider can be prompted to update the questions every 5 years only if opioids are prescribed. Once the response to a question is positive, the response does not need to be updated. In this way, a team approach can be used to determine and maintain opioid risk for the patient population.

Cultural and Structural Change

The healthcare system has overcome race and gender biases in the past and has incorporated other sensitive questions into the documentation of routine history and physical examinations. In the 1980s, medical students were taught not to describe patients as "obese," yet when gastric bypass surgery became available as a treatment, documentation of obesity in the medical record became standard clinical practice. Similarly, during the HIV epidemic in the 1980s, students and residents were taught to take detailed sexual histories to better care for patients and to define the extent of their disease. More recently, changes to the EMR have been made to accommodate sensitivities regarding how to appropriately address transgender patients. America's prescription epidemic is a result of a similar evolving cultural pathology that must be addressed and requires new standards of care and new modes of communication. Providers need to develop standard scripts to address this discomfort. Suggested scripts include the following:

1. In order to prescribe opioid pain medication, I need to ask some sensitive questions to help protect you from complications.
2. Because of the risk of opioid medication, it is now standard practice that we assess the risk of addiction and there are some important questions that need to be asked about your psychiatric history.
3. Since this surgery may require opioid pain medication, I need to ask you a few questions to assess risks. Let's go over them together.
4. It's now routine we ask these questions before prescribing opioids in order to protect all our patients as a whole. Some might be sensitive for you. It is okay if you do not want to answer them all.
5. Because there is a high prevalence of child sexual abuse and that abuse can increase your risk for taking opioid pain medications, I need to ask if you were ever sexually abused as a child.
6. Have you ever had a history of sexual abuse?
7. As a child did anyone ever touch you in sexual ways?

The ACOG provides the following recommendations for asking patients questions about sexual abuse [11]:

1. Make the question "natural." When physicians routinely incorporate questions about possible sexual abuse, patients will develop increased comfort.
2. Normalize the experience. Physicians may offer explanatory statements, such as "About one woman in five was sexually abused as a child. Because these

experiences can affect health, I ask all my patients about unwanted sexual experiences in childhood."
3. Give the patient control over disclosure. Ask every patient about childhood abuse and rape trauma, but let her control what she says and when she says it in order to keep her emotional defenses intact.
4. If the patient reports childhood sexual abuse, ask if she has disclosed it in the past or sought professional help. Revelations may be traumatic for the patient. Listening attentively is important because excessive reassurance may negate the patient's pain. The physician should consider referral to a therapist.

Addressing the opioid epidemic requires providers to compassionately change their thinking about properly screening all patients for addiction, including women who have greater risk. Evidence-based tools are available that reflect the pathology in the community. These tools are based on a reality that can no longer be overlooked. It is understandable that various providers have preconceived notions and routines based on habit and culture, but pathology in our history and culture needs to be dealt with in a smart and structured manner. Superficial assumptions about women's health need to be replaced with evidence-based medicine and a move from the realm of specialized care (obstetrics and gynecology) into mainstream medicine and surgery. Provider biases should be acknowledged and confronted by incorporating these tools into routine care and healthcare structures.

Key Points

- The Opioid Risk Tool is a discreet method of conveying sensitive information about a patient's psychiatry history with a number value.
- Included in an opioid risk assessment should be the Opioid Risk Tool score, a pain history, an opioid history, a psychiatry history, a urine toxicology screen, calculation of the oral morphine equivalent dose, and a check of the Prescription Monitoring Program.
- Healthcare systems must address gender biases structurally by applying evidence-based protocols to routine care.
- Deaths from prescription painkiller overdoses among women have increased more than 400% since 1999, compared to 265% among men.
- Women are more likely to have chronic pain, are more likely to be prescribed painkillers, and are given higher doses for longer periods of time than men. Women become dependent more quickly than men.
- Opioids affect judgment, memory formation, and emotional control by causing neuroplastic changes in the prefrontal lobe, the nucleus accumbens, the ventral tegmental area, the amygdala, the periaqueductal grey zone, and the rostral ventral medulla of the midbrain.
- Child sexual abuse has been linked to a lack of self-protection in adults and is a risk factor for the initiation and escalation of substance use among women.

- Approximately one in five women experienced child sexual abuse.
- Prescribing opioids to a patient with an unknown history of child abuse places that patient at risk for a lifetime of addiction. This fact underscores the importance of this important screening before a prescription is written.
- The Opioid Risk Tool score is based on the responses to five questions about personal history of substance use, family history of substance use, history of psychological disease, age, and history of preadolescent sexual abuse.
- Preadolescent sexual abuse and domestic violence questions are routine in pediatrics, obstetrics and gynecology, and emergency department medicine and should be routine to any provider who prescribes opioids.
- Validated evidence-based tools must be used to assess high-risk medications before prescribing and should be incorporated into routine care and into the healthcare structure. The Opioid Risk Tool score can be used as a stop/pause/think measure that alerts the provider to determine if a full risk-benefit analysis needs to be performed. The score is determined by a previous provider and communicates risk in a sensitive fashion from visit to visit, from previous physician to present physician, from outpatient setting to inpatient setting, from the psychiatrist to the emergency department physician or hospitalist, and vice versa.
- It is a minimum standard of care that the risk of addiction should be assessed prior to giving opioids to a patient. The Opioid Risk Tool meets that minimum standard.
- America's prescription epidemic is a result of an evolving cultural pathology that must be addressed. It requires new standards of care and new modes of communication. Providers need to develop standard scripts to address their discomfort.

References

1. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med. 2005;6(6):432–42.
2. Trechak AA. On cultural and gender bias in medical diagnosis. Multicult Educ. 1999;7(2):41.
3. Holdcroft A. Gender bias in research: how does it affect evidence based medicine? J R Soc Med. 2007;100(1):2–3. doi:10.1258/jrsm.100.1.2.
4. Duarte DF. Opium and opioids: a brief history. Rev Bras Anestesiol. 2005;55(1):135–46.
5. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology. 2008;33(1):166–80.
6. Martin L, Laderman M, Hyatt J, Krueger J. Addressing the opioid crisis in the United States. IHI Innovation Report. Cambridge, MA: Institute for Healthcare Improvement; 2016. http://www.ihi.org/resources/Pages/Publications/Addressing-Opioid-Crisis-US.aspx?utm_campaign=tw&utm_source=hs_email&utm_medium=email&utm_content=32920825&_hsenc=p2ANqtz-_8KaK1j-okcapyVh9HSIFKr8A4kaadvwpmLjK9McIUktS_NFXhq8GrP7FdlQ94rJ6GtQhwAufw6H1N_O3H2TjdcBz4zA&_hsmi=32920016. Accessed 9 Dec 2016
7. Meyer R, Patel AM, Rattana SK, Quock TP, Mody SH. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul Health Manag. 2014;17(6):372–87. doi:10.1089/pop.2013.0098.

8. Prescription painkiller overdoses. Centers for Disease Control and Prevention. 2013. https://www.cdc.gov/vitalsigns/PrescriptionPainkillerOverdoses/index.html. Accessed 2 Mar 2017.
9. Weiss R. Why do people with addictions seek to escape rather than connect? A look at the approach to addiction treatment. Consultant. 2016;56(9):786–90.
10. Cohen LR, Tross S, Pavlicova M, Hu MC, Campbell AN, Nunes EV. Substance use, childhood sexual abuse, and sexual risk behavior among women in methadone treatment. Am J Drug Alcohol Abuse. 2009;35(5):305–10. doi:10.1080/00952990903060127.
11. Committee on Health Care for Underserved Women, American College of Obstetricians and Gynecology, Adult Manifestations of Childhood Sexual Abuse, Number 498. August 2011. https://www.acog.org/-/media/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/co498.pdf?dmc=1&ts=20170223T1626301600. Accessed 2 Mar 2017.

Chapter 16
Nonopioid and Adjuvant Analgesics for Acute Pain Management

Michele L. Matthews, Raymond Melika, and Yulia Murray

Abbreviations

APAP	Acetaminophen
CNS	Central nervous system
COX	Cyclooxygenase
CV	Cardiovascular
CYP	Cytochrome P450
GI	Gastrointestinal
IM	Intramuscular
IN	Intranasal
IV	Intravenous
NAPQI	*N*-acetyl-*p*-benzoquinone imine
NSAID	Nonsteroidal anti-inflammatory drug

Introduction

Acute pain can be attributed to an identifiable cause including trauma or surgery and is a result of actual or potential tissue damage that lasts for less than 3 months. Acute pain usually resolves as the underlying injury heals, although some patients may experience pain without actual tissue damage, as in the case of muscle cramps [1]. Acute pain can be nociceptive and/or neuropathic in nature. Nociceptive pain is further delineated into somatic or visceral causes, with somatic pain originating from the bone, joint, muscle, or skin while visceral pain results from distension or

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inflammation due to excess activity at visceral afferent nerve fibers. Somatic pain is usually described as aching or throbbing, and visceral pain is cramping, heavy, and squeezing in nature. Neuropathic pain arises from abnormal sensory processing within the peripheral or central nervous system (CNS) and is described as sharp, shooting, electrical, or burning.

The subjective nature of pain warrants an individualized approach to both assessment and management. Objective physical signs such as tachycardia and diaphoresis may be associated with acute pain; however, these should not be considered diagnostic. The initial assessment of acute pain should be based on the patient's report through the use of pain intensity scales, such as the verbal numeric rating scale (e.g., 0 = no pain to 10 = worst pain imaginable). While the assessment of pain intensity is important, approach to treatment should be based on comprehensive patient assessment that includes history of present illness, medical history, current medications, drug allergies/intolerance, prior response to analgesics, and physical examination. In patients with difficulty self-reporting pain, the following hierarchy of assessment can be considered: 1. Search for potential causes of pain, 2. Look for pain behaviors and consider use of evidence-based, valid, and reliable behavioral pain tools for the selected populations (e.g., Behavioral Pain Scale, Critical-Care Pain Observation Tool) [2]. 3. Obtain proxy or surrogate reports from caregivers, and 4. Consider an analgesic trial if potential benefits outweigh risks [3, 4]. Pain should be routinely reassessed, and the plan of care should be clearly documented.

Patient education that is individualized and supportive can have several benefits for the management of perioperative pain, including reduced opioid consumption and reduced length of stay after surgery in those with more intensive needs due to medical or psychological comorbidities or social factors [5]. There is no evidence that basic educational interventions (e.g., provision of written materials) are more effective than intensive, multicomponent interventions (e.g., supervised education, phone calls), further supporting the importance of an individualized approach. Information that should be provided to the patient and family should be age appropriate, geared to the appropriate level of comprehension, general health literacy, and cultural and linguistic competency, and supported by timely opportunities to ask questions and receive authoritative and useful answers [6]. Patients should be counseled on how pain is reported and assessed, realistic goals for pain relief, options for treatment, and addressing underlying misperceptions.

General Principles of Analgesics for Acute Pain

The goals of therapy for the management of acute pain are to provide optimal analgesia while minimizing adverse effects from therapy. Drug therapy is often the mainstay of acute pain management, and clinicians should consider the following before initiating analgesics: pain etiology and duration, patient age, comorbidities, potential for adverse outcomes, potential drug interactions, adherence, complexity

of the regimen, costs, risks for misuse, abuse, or intentional or unintentional overdose, and patient knowledge of risks of treatment and nonpharmacologic alternatives [5].

Drugs used for pain management are categorized as nonopioid analgesics (e.g., acetaminophen), adjuvant analgesics (e.g., local anesthetics), and opioid analgesics. With regard to choice of analgesic therapy, it is important to consider that nociceptive pain is usually responsive to pharmacologic therapies that target the ascending and descending pathways at the point of noxious stimuli exposure (e.g., acetaminophen, opioids), while neuropathic pain management includes the use of adjuvant analgesics (e.g., anticonvulsants). However, there is significant variability in individual response to analgesics, and choice of therapy should foremost include patient-specific consideration of balancing efficacy with tolerability, even if discordant with available evidence. Combining analgesics with different mechanisms of action as a multimodal approach to therapy may result in enhanced analgesia while limiting dose-related toxicities due to the synergistic properties of the regimen. Caution should be exercised when considering the use of co-analgesics in pediatric or older adult patients due to the potential for increased risk of adverse effects.

This chapter will focus on the role of nonopioid and adjuvant analgesics for the management of acute pain. Table 16.1 summarizes these agents based on formulations, common dosing strategies, and adverse effects.

Nonopioid Analgesics

Acetaminophen

Acetaminophen (APAP) has been used for its analgesic as well as anti-pyretic properties for decades. The exact mechanism by which APAP acts remains unknown. Often improperly classified as a nonsteroidal anti-inflammatory drug (NSAID), it has no clinically significant anti-inflammatory effect at therapeutic doses. It was previously theorized that APAP acted by inhibiting cyclooxygenase (COX)-1 and COX-2, much like NSAIDs. However, select animal data implicates the COX-3 enzyme as the likely primary site of inhibition of prostaglandin synthesis, which affords APAP its analgesic and anti-pyretic properties [7].

When administered orally, immediate-release APAP reaches maximum plasma concentrations within 1 h in adults and has an oral bioavailability of 85–98%. APAP is largely metabolized by the liver by the process of conjugation with glucuronide or sulfate respectively, or through oxidation by the means of Cytochrome P450 (CYP) 2E1. Oxidation by the CYP pathway produces the hepatotoxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI) which is then conjugated with glutathione to produce the non-toxic metabolites cysteine and mercapturic acid. Because of this preferentially hepatic metabolism, patients with liver damage are exposed to higher risk of APAP toxicity, particularly due to NAPQI accumulation. In healthy adults, APAP has a half-life of roughly 2.4 h.

Table 16.1 Summary of nonopioid and adjuvant analgesics for the management of acute pain

Drug/Therapeutic class	Formulation(s)	Adult Dosing for Acute Pain	Adverse Effects
Acetaminophen	Oral, rectal, IV	Oral: 500–1000 mg every 6 h as needed Rectal: 650 mg every 4 to 6 h (MAX 6 suppositories/24 h) IV: <50 kg: 15 mg/kg every 6 h or 12.5 mg/kg every 4 h ≥50 kg: 1000 mg every 6 h or 500 mg every 4 h MAX 1000 mg per dose; MAX 3000–4000 mg per day	Common: nausea/vomiting Serious: liver failure
NSAIDs			
Ketorolac	Oral, IV, IM, IN	Oral: <65 years old: 20 mg followed by 10 mg every 4 to 6 h as needed, MAX 40 mg/day ≥65 years old: 10 mg once followed by 10 mg every 4 to 6 h as needed, MAX 40 mg/day IV: <65 years old: 30 mg as a single dose or 30 mg every 6 h, MAX 120 mg/day ≥65 years old: 15 mg as a single dose or 15 mg every 6 h; MAX 60 mg/day IM: <65 years old: 60 mg as a single dose or 30 mg every 6 h; MAX 120 mg/day ≥65 years old: 30 mg as a single dose or 15 mg every 6 h; MAX 60 mg/day IN: <65 years old: 1 spray (15.75 mg) in each nostril (total dose 31.5 mg) every 6 to 8 h; MAX 126 mg/day Total duration of use of oral, IV, and/or IM dosing is not to exceed 5 days	Common: nausea/vomiting, heartburn, edema, hypertension, nasal irritation (IN) Serious: gastrointestinal (GI) bleeding, renal toxicity, cardiovascular (CV) events
Ibuprofen	Oral, IV	Oral: 400–800 mg every 4–6 h as needed IV: 400 to 800 mg every 6 h as needed, infused over at least 30 min MAX 3200 mg/day	Common: nausea/vomiting, heartburn Serious: GI bleeding, renal toxicity, CV events

(continued)

Table 16.1 (continued)

Drug/Therapeutic class	Formulation(s)	Adult Dosing for Acute Pain	Adverse Effects
Celecoxib	Oral	400 mg once plus one additional 200 mg dose if needed on the first day; maintenance, 200 mg twice a day as needed	Common: nausea, diarrhea, hypertension Serious: GI bleeding, renal toxicity, CV events
Anesthetics			
Bupivacaine	Parenteral, multiple injection types	Dosage varies with anesthetic procedure, area to be anesthetized, vascularity of the tissues, number of neuronal segments to be blocked, depth of anesthesia and degree of muscle relaxation required, duration of anesthesia desired, individual tolerance, and physical condition of the patient Intrapleural: 10 to 30 mL bolus of 0.25%, 0.375%, or 0.5% every 4 to 8 h Epidural: continuous infusion, 6.25 to 18.75 mg/hr. as a 0.0625% to 0.125% solution	Common: numbness Serious: CV events, mental status changes
Lidocaine	Parenteral, multiple injection types	Dosage varies with anesthetic procedure, area to be anesthetized, vascularity of the tissues, number of neuronal segments to be blocked, depth of anesthesia and degree of muscle relaxation required, duration of anesthesia desired, individual tolerance, and physical condition of the patient IV regional block: 10 to 60 mL of a 0.5% solution for a total dose of 50 to 300 mg, MAX 4 mg/kg dose, MAX 300 mg total dose IV infusion: 1.5 mg/kg followed by 2 mg/kg/h intraoperatively	Common: numbness Serious: CV events, mental status changes

(continued)

Table 16.1 (continued)

Drug/Therapeutic class	Formulation(s)	Adult Dosing for Acute Pain	Adverse Effects
Gabapentinoids			
Gabapentin	Oral	300 to 1200 mg as 1 dose administered 1 to 2 h prior to surgery	Common: sedation, ataxia, edema, fatigue Serious: worsening mood
Pregabalin	Oral	100 or 300 mg preoperatively, or 150 or 300 mg preoperatively followed by the same dose 12 h later	
Ketamine	IV	Preoperative bolus of 0.5 mg/kg followed by an infusion at 10 mcg/kg/min intraoperatively, with or without a postoperative infusion at a lower dose 0.1–0.2 mg/kg bolus followed by 0.1–0.3 mg/kg h	Serious: hallucinations, nightmares, dissociative symptoms
Alpha-2 agonists			
Clonidine	Oral, transdermal patch, parenteral	Dosage varies based on indication Oral: 75–300 mcg/day Transdermal patch: up to 300 mcg/day Epidural: 30 mcg/h. and titrate as required for pain relief, limited experience with dose >40 mcg/h. Intrathecal: 75–950 mcg/day	Adverse effects may be more prominent with oral administration vs transdermal Common: sedation, dry mouth, dizziness, drowsiness, fatigue, headache Epidural: hypotension, orthostatic hypotension
Dexmedetomidine	IV	Perioperative bolus dose of 0.5–1 mcg/kg, with or without continuous infusion of 0.5–2 mcg/kg per hour	Hypotension, bradycardia, systolic hypertension, tachycardia, respiratory depression, agitation, nausea, constipation

Adapted from references [5, 12, 19, 26, 27, 39–41]

The efficacy of APAP for perioperative pain management has been demonstrated in studies involving orthopedic surgeries, and use as a component of multimodal analgesia may reduce postoperative opioid requirements [8]. When used to treat acute postoperative pain, there is evidence to suggest that a single 500 mg–1000 mg dose of intravenous (IV) APAP is associated with roughly 4 h of pain relief [9]. The buccal formulation of APAP has also shown to be non-inferior to IV APAP for the treatment of acute traumatic pain at as low as 125 mg per dose [10]. Use of oral

APAP for acute postoperative pain is associated with better outcomes when used adjunctively to a nonsteroidal anti-inflammatory drug (NSAID). This multi-drug approach has proven to be more efficacious than either 1000 mg oral APAP or 400 mg oral ibuprofen alone [11]. For the management of acute low back pain, there was no difference between scheduled or as-needed APAP compared to placebo with regard to pain, function, or risk of adverse effects after 4 weeks of treatment [12].

The maximum daily dose of APAP is 4000 mg/day in the absence of hepatic or renal disease or concomitant drugs or substances (e.g., alcohol) that can increase the risk of hepatic injury. The use of APAP should be limited to less than 2000 mg/day in hepatic disease, and liver function should be monitored closely. The maximum single dose recommended for the management of mild to moderate pain is 1000 mg. Due to the notably high bioavailability of APAP, there is no recommended dose adjustment when converting from an oral dose to an IV dose.

APAP is generally regarded as a safe drug. When taken by healthy adults within therapeutic doses, adverse effects may include a mild and reversible elevation in liver function tests. Patients may also experience nausea, vomiting, or pruritus, although such occurrences are seldom noted. At higher doses, hepatotoxicity becomes a concern leading to risk of death, and acute overdoses can be treated with N-acetylcysteine and hemodialysis.

Non-Steroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are agents which produce an anti-inflammatory, anti-pyretic, and analgesic effect without steroidal activity. They have become a mainstay of pain therapy due to their wide availability in multiple formulations and dosages. The mechanism of action for NSAIDs is decreased production of prostaglandins through the reversible inhibition of the COX enzymes. There are various subclasses of NSAIDs, and various drugs within those subclasses, with a notable spectrum of COX selectivity. There are some agents which broadly act on both COX-1 and COX-2, and other agents which tend to favor COX-2. Although the agents seem to implicate little-cross tolerance, there is no evidence to suggest that one agent is better than the other for the purposes of analgesia [13].

The most common concerns that arise related to the use of NSAIDs are the decreased protection of the gastrointestinal (GI) lining, as well as the increased cardiovascular (CV) risk due to the inhibition of prostaglandins produced by the inhibition of COX-2. Those NSAIDs which preferentially inhibit COX-2 are designed to have a lower risk of GI adverse events, yet they can have a significantly higher risk of CV complications. Another concern with these agents is the risk of renal impairment due to the decreased prostaglandin-induced vasodilation of the afferent arterioles of the kidney, causing renal hypo-perfusion. Thus, NSAIDs should be avoided in patients with significant renal impairment. Other adverse effects noted across the class include nausea, vomiting, and increased risk of bleeding, particularly when used concomitantly with serotonergic agents.

Ketorolac

Ketorolac is an acetic acid derivative which has been used for various types of acute pain and is available in oral, IV, intramuscular (IM), rectal, subcutaneous, ophthalmic, and intranasal (IN) formulations. It reaches maximal plasma concentrations about 30–60 min after oral, subcutaneous, rectal or IM administration, and has a 100% oral bioavailability [14]. Intramuscular ketorolac has been studied at doses of 10, 30, and 60 mg, with significant evidence that all of these doses provide acute pain relief when compared to placebo. Oral ketorolac was studied at doses of 5, 10, and 20 mg with similar evidence for analgesia. There is no evidence to support significant differences in analgesia between the oral and IM formulations of ketorolac along the dose ranges noted [15]. Another study evaluated IV ketorolac 30 mg (15 mg in patients aged greater than 65) post-lumbar decompressions surgery and found that ketorolac significantly decreased pain scores on a visual analogue scale compared to placebo at 0, 4, 8, 12, and 16 h post-surgery [16]. There is also data to suggest that when used preoperatively, ketorolac can significantly reduce postoperative pain intensity. In a meta-analysis of 13 randomized, controlled trials, it was found that a perioperative (either preoperative or intra-operative) IV dose of ketorolac 60 mg was associated with significant postoperative pain relief as well as a reduction in postoperative nausea and vomiting, although there was no statistical significance for the 30 mg dose [17].

Ketorolac is the first NSAID to be developed into an intranasal (IN) formulation, having similar pharmacokinetics to oral, IM, and IV formulations. The IN formulation has also shown promising analgesic efficacy when used postoperatively in procedures ranging from major abdominal/orthopedic surgery to minor molar extractions. In a meta-analysis of four studies, it was shown that a single 31.5 mg dose of IN ketorolac provided significant pain relief at 6 h, lasting as long as 48 h [18].

The safety profile for ketorolac differs slightly from that of other NSAIDs. The increased risk of GI bleeding and hemorrhage indicates the avoidance of ketorolac peri-operatively, and further mandates that clinicians exercise caution when using ketorolac postoperatively, particularly in hemodynamically unstable patients. Since ketorolac and its metabolites are primarily excreted through the kidney, clinicians must be wary of changes in a patient's renal function, and adjust the use of ketorolac accordingly. The administration of ketorolac should be restricted to a maximum of 5 days at a time. This principle holds true when administering the IM, IV, or oral formulation, or any combination of these formulations [19].

Ibuprofen

Along the spectrum of COX selectivity, ibuprofen seems to inhibit COX-1 at a rate of 2.5 times that of COX-2. In theory, it is more likely to be associated with GI concerns than with CV ones; however, there is evidence that ibuprofen confers similar CV risks in comparison to COX-2 selective NSAIDs [20]. Doses of IV ibuprofen that are commonly utilized for the treatment of acute postoperative pain include 400

or 800 mg, infused over 30 min, although there is evidence to suggest that doses as low as 100 and 200 mg can significantly decrease postoperative pain [21].

Ibuprofen has been evaluated as an opioid-sparing agent, and when studied for its ability to decrease postoperative patient-controlled morphine use, patients administered 800 mg of IV ibuprofen every 6 h following abdominal or orthopedic surgery used less than half the amount of morphine within the first 24 postoperative hours, compared to the placebo group. In this same study, it was found that patients receiving ibuprofen experienced a twofold reduction in pain upon movement, and a near four-fold reduction in pain during rest [22]. There is also some data suggesting that preemptive analgesia with preoperative 800 mg IV Ibuprofen resulted in a significant reduction in postoperative pain scores in the first 6 to 28 postoperative hours [23].

Ibuprofen can be considered as part of a multimodal approach for analgesia. This can be useful, not only from the perspective of increased analgesia, but also decreased cost, as well as minimizing adverse events. In a systematic review, a combination of 400 mg of ibuprofen and 1000 mg of APAP was compared to each respective agent alone, and was found to be significantly more effective as a combination. Further, while two of the studies showed no difference in adverse events between the treatment groups, one study found evidence that the combination of ibuprofen and APAP resulted in less adverse events compared to ibuprofen monotherapy [24].

Celecoxib

Celecoxib is a selective inhibitor of COX-2 which can produce comparable analgesia to nonselective NSAIDs with less GI-related complications and is less likely to precipitate bleeding through inhibition of platelet aggregation. However, celecoxib use has been associated with major CV events and should be used cautiously in patients with cardiac comorbidities.

In a meta-analysis studying the effects of a celecoxib on acute pain, both a 200 mg and a 400 mg oral dose of celecoxib resulted in significant pain reduction in both dental and postsurgical pain over a period of 4–6 h. The 400 mg dose was found to be significantly more effective than the 200 mg dose, with comparable efficacy to a 400 mg dose of ibuprofen [25].

Adjuvant Analgesics

Local Anesthetics

The local anesthetics are those agents which, by virtue of their formulation or chemical composition, are not systemically absorbed to any clinically relevant degree; their effect is intended to be exerted only on the area to which they are applied or injected. As anesthetics, they produce a numbing effect, decreasing sensation in areas of contact. Bupivacaine and lidocaine are two commonly used local anesthetics

that have similar structures and function and are often used for the treatment of acute pain. Both of these agents act by reversibly inhibiting sodium channels of the neurons involved in the pain pathway, stopping depolarization and intercepting the transition of the painful impulse. The sensations affected by these agents happen in a generally stepwise fashion. First, sensation to pain decreases, followed by temperature, touch, proprioception (self-spatial perception), and skeletal muscle tone [26].

At clinically accepted doses for treating pain, there is very little concern for systemic absorption of either lidocaine or bupivacaine. However, at higher doses, systemic absorption increases the risk of CNS and CV adverse effects. Local anesthetics can inhibit neural impulsivity in the CNS leading to CNS depression, as well as in the heart sinuses and cardiac myocytes leading to decreased cardiac excitability and contractility. For this reason, it is imperative that proper doses are administered using the lowest necessary dose, and that inadvertent intravascular administration be avoided [27]. Further, when injecting a patient with a local anesthetic, the clinician should carefully monitor the patient's cardiac, respiratory, and neurological vital signs for any changes.

Lidocaine

Lidocaine is an amide anesthetic that works locally. Large volumes for injection can often be found formulated with epinephrine, in order to vasoconstrict the blood vessels around the site of injection, thereby limiting the clearance of lidocaine from the injection site. When used in normal healthy adults, lidocaine doses of no greater than 7 mg/kg of body weight should be injected (with a 500 mg ceiling). When formulated with epinephrine, the recommendation decreases to 4.5 mg/kg of body weight (with a 300 mg ceiling.) If administered through intravenous local routes, the dose should not exceed 4 mg/kg [26]. Depending on the procedure and the location of administration, there are various recommended concentrations of lidocaine used, as well as various lengths of infusions.

There is some data to indicate that postoperative use of a lidocaine patch resulted in less pain upon movement, as well as its effectiveness in treating acute pain post-laparoscopic surgery. However, other studies have demonstrated a lack of efficacy of the patch post total knee arthroplasty, and most data regarding its efficacy is outdated [28]. A recent meta-analysis of five studies regarding the use of the lidocaine 5% patch for acute pain management found no significant benefit over placebo in the decrease of opioid consumption, postoperative pain intensity, or length of hospital stay [29]. A similar result was found in a randomized, controlled trial analyzing the use of lidocaine 5% patch for treatment of acute pain following robotic cardiac surgery [30].

Bupivacaine

Similar to lidocaine, bupivacaine is an amide-based local anesthetic. However, unlike lidocaine, it is only available in the form of an injection, which can also be formulated with epinephrine. Bupivacaine has a relatively long half-life (2.7 h)

when compared to other local anesthetics [27]. Newer formulations of bupivacaine have emerged with liposomal encapsulations in order to further increase its duration of action. In the liposomal formulations, plasma concentrations have been noted after 72 h [31]. Bupivacaine has been used for nerve blocks, infiltration anesthesia, as well as epidurals and caudal anesthesia. An additional benefit to the use of bupivacaine is its selectivity to sensory neurons over motor neurons, making it an excellent regional anesthetic agent in select settings (e.g., obstetrics) [32]. Bupivacaine doses vary and are dependent on the route of administration and clinical indication. In post-thoracotomy patients, intrapleural bupivacaine was shown to be significantly more effective at decreasing pain than intrapleural morphine, as well as significantly more effective at decreasing the need for additional opioids [33]. When used for postoperative pain management following total knee replacement, liposomal bupivacaine demonstrated decreased pain scores, as well as decreased need for medications for breakthrough pain, and shortened hospital stay [34]. As compared to lidocaine, bupivacaine showed greater efficacy in decreasing postoperative nasopharyngeal pain [35]. Bupivacaine has also demonstrated analgesic efficacy in the setting of cholecystectomy [36], breast surgery [37], and thyroidectomy [32]. In comparing the clinical differences of liposomal bupivacaine to continuously infused intraperitoneal bupivacaine, most studies show no significant benefit to the liposomal formulation, or at least none which justify the difference in cost [31, 38].

Anticonvulsants: Gabapentinoids

Anticonvulsants exert an analgesic effect by reducing neuronal hyperexcitability within the CNS through various mechanisms. These agents are often utilized in the setting of neuropathic pain and migraine prophylaxis and are increasingly implemented as part of a multimodal approach in the perioperative setting for their opioid-sparing effects. Specifically, gabapentin and pregabalin have been studied in the setting of acute pain management and have both been found to be effective for reducing pain intensity as well as opioid requirements when administered as a preoperative dose (e.g., 600 or 1200 mg of gabapentin or 150 or 300 mg of pregabalin, administered 1–2 h preoperatively). Select trials also found postoperative dosing (e.g., gabapentin 600 mg as a single or in multiple doses and pregabalin 150 or 300 mg after 12 h) to be effective [5].

In a meta-analysis of randomized controlled trials of patients undergoing elective primary total knee arthroplasty, no difference in pain scores was found at 12, 24, 48, or 72 h following the surgical procedure for neither gabapentin nor pregabalin compared to placebo, although a small reduction in cumulative opioid consumption was observed at 48 h [39]. Although there is conflicting evidence with regard to the use of gabapentinoids for perioperative pain, the use of these drugs has been supported by practice guidelines, particularly for patients undergoing major surgery [5]. There are few differences between gabapentin and pregabalin with the exception of decreasing bioavailability with increasing oral doses of gabapentin due to saturable absorption.

Both medications are only available in oral dosage forms and require dose adjustment in the setting of renal impairment. The potential for CNS-related adverse effects such as dizziness and sedation should be considered before initiating therapy.

Ketamine

The *N*-methyl-D-aspartate (NMDA) receptor has been implicated in playing an important role in inflammation and central sensitization which could lead to abnormal pain sensations (e.g., hyperalgesia). Medications that block this receptor include ketamine, dextromethorphan, memantine, and amantadine. These drugs have been studied for neuropathic pain states with inconclusive evidence to support their use [40]. Perioperative use of ketamine at varying doses (e.g., boluses up to 2 mg/kg and infusions up to 2 mg/kg/h) and routes of administration has been associated with decreased pain scores, reduced analgesic use, and decreased risk of persistent postsurgical pain [5].

Ketamine may be useful for acute pain management in highly opioid-tolerant patients or those who have difficulty tolerating opioids. The adverse effect profile of ketamine includes the risk of hallucinations, nightmares, and dissociative symptoms; therefore, due to the narrow therapeutic index, use should be reserved for clinicians with experience in its use.

Alpha-2 Agonists

Clonidine

Clonidine is a centrally acting, selective alpha-2 adrenergic receptor agonist, and in clinical practice it is primarily used for the management of hypertension but also has established utility in the management of acute pain during the perioperative period, treatment and prevention of iatrogenic opioid abstinence syndrome, sedation, and chronic pain [41–43]. Clonidine is a highly lipid soluble compound, and therefore is able to cross the blood–brain barrier into the cerebrospinal fluid and produce a central analgesic effect. Clonidine reaches approximately 50% of total plasma concentration in the cerebrospinal fluid. With regard to its elimination, clonidine is eliminated in urine in the unchanged form. Oral bioavailability of clonidine is about 70 to 80% and it is rapidly absorbed within 30 min after administration. Peak plasma clonidine levels are attained in approximately 1–3 h.

It is important to note that after intravenous administration of clonidine it follows a biphasic disposition with a distribution half-life of about 20 min and elimination half-life of about 12–16 h (elimination half-life is severely prolonged in patients who have a significant renal impairment). Clonidine has been utilized in intravenous, epidural, intrathecal, oral, and transdermal routes of administration in the management of acute pain. It has been demonstrated that systemic administration of clonidine in

the postoperative period has led to lower morphine requirements and/or delayed time to morphine administration, as well as reduced overall pain scores [41]. Clonidine has also been utilized either alone or as an adjunct to local anesthetics or morphine in intrathecal anesthesia. Intrathecal use of clonidine alone or in conjunction with local anesthetics agents was shown to be effective; however, intrathecal administration of clonidine with morphine resulted in mixed outcomes. Review of available literature has also demonstrated that epidural administration of clonidine requires further investigation [41]. If clonidine is used for the management of acute pain, it is very important to monitor patients for the development of hypotension and bradycardia, as these are the most common adverse effects associated with the use of alpha-2 agonists. Abrupt discontinuation of clonidine should be avoided as it can lead to the rebound hypertension and agitation. When a decision to discontinue clonidine is made, it is recommended to gradually taper the medication off.

Dexmedetomidine

Dexmedetomidine is also a centrally active, selective alpha-2 adrenergic receptor agonist; however, compared to clonidine, dexmedetomidine has about eight times higher affinity to the alpha-2 adrenergic receptors [41]. Dexmedetomidine is currently approved for short-term sedation of intubated adults and surgical sedation of nonintubated patients. Dexmedetomidine has also been utilized in the management of treatment and prevention of iatrogenic opioid abstinence syndrome, agitation, delirium, and pain [41, 42, 44]. Dexmedetomidine crosses the blood–brain barrier and reaches about 10% of the plasma concentration in the cerebrospinal fluid.

Dexmedetomidine is primarily excreted by the kidneys and has a half-life of approximately 2 h. Dexmedetomidine has not been evaluated in the literature as extensively as clonidine for pain management, but it has been established that dexmedetomidine can provide opioid-sparing qualities [41]. When used as part of the multimodal analgesia in postoperative patients, dexmedetomidine use may help to reduce opioid use but not necessarily lower overall pain scores. It is not recommended to use dexmedetomidine as a single mode of analgesia [41]. If dexmedetomidine used, hemodynamic parameters must be monitored. Once dexmedetomidine can be discontinued; a wean over 12–24 h is usually recommended.

Approaches to Transitions of Care

Appropriate communication and coordination with the care team is important for patients requiring management of acute pain upon discharge. Patients should be educated on expectations related to recovery and how to safely manage their analgesic regimen to optimize pain relief and ability to return to usual activity. Detailed medication reconciliation should be performed to avoid potential duplications in therapy and to ensure the

patient's understanding on how to properly administer medications at home. Another component to consider at the time of discharge is patient accessibility to the pharmacy and the patient's ability to afford the prescribed medications. Certain medications might not always be available for immediate pick up at the local pharmacy and special order might need to be placed, which might delay the time the patient will receive prescribed regimen at home. Patient-specific insurance coverage and specific medication formulary should also be taken into consideration, and certain medications might require prior authorization. All members of the healthcare team should be involved in safely and efficiently transitioning the patient from the inpatient to the ambulatory setting.

Summary

The approach to acute pain management should be individualized and should integrate the use of multimodal analgesia whenever possible. Nonopioid and adjuvant analgesics can be used in combination with opioid therapy to minimize adverse effects and facilitate achievement of therapeutic goals that are appropriate for the patient and the clinical scenario. Patient and caregiver education and appropriate communication and coordination of care can have an important role in ensuring safe and effective acute pain management.

Key Points

- Drug therapy is often the mainstay of acute pain management, and clinicians should consider the following before initiating analgesics: pain etiology and duration, patient age, comorbidities, potential for adverse outcomes, potential drug interactions, adherence, complexity of the regimen, costs, risks for misuse, abuse, or intentional or unintentional overdose, and patient knowledge of risks of treatment and nonpharmacologic alternatives.
- Nonopioid and adjuvant analgesics can be used in combination with opioid therapy to minimize adverse effects and facilitate achievement of therapeutic goals that are appropriate for the patient and the clinical scenario.
- There is significant variability in individual response to analgesics, and choice of therapy should foremost include patient-specific consideration of balancing efficacy with tolerability, even if discordant with available evidence.
- Individualized patient education can have several benefits for the management of acute pain, particularly in the perioperative setting, by potentially minimizing the use of high risk medications and reducing length of hospital stay.
- In patients transitioning from the inpatient to the ambulatory setting, appropriate communication and coordination with the care team is important for patients requiring management of acute pain upon discharge to optimize analgesia and return to usual activity.

References

1. International association for the study of pain. Pain terms, a current list with definitions and notes on usage. Available at: http://www.iasp-pain.org/Taxonomy. Accessed 12 Oct 2016.
2. Gélinas C, Puntillo KA, Joffe AM, Barr J. A validated approach to evaluating psychometric properties of pain assessment tools for use in nonverbal critically ill adults. Semin Respir Crit Care Med. 2013;34(2):153–68.
3. Herr K, Coyne PJ, McCaffery M, Manworren R, Merkel S. Pain assessment in the patient unable to self-report: position statement with clinical practice recommendations. Pain Manag Nurs. 2011;12(4):230–50.
4. McCaffery M, Herr K, Pasero C. Assessment. In: Pasero C, McCaffery M, editors. Pain assessment and pharmacologic management. St. Louis, MO: Mosby Elsevier; 2011.
5. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17(2):131–57.
6. IOM (Institute of Medicine). Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press; 2011.
7. Chandrasekharan N, Dai H, Roos K, Evanson N, Tomsik J, Elton T, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci. 2002;99(21):13926–31.
8. Sinatra RS, Jahr JS, Reynolds L, et al. Intravenous acetaminophen for pain after major orthopedic surgery: an expanded analysis. Pain Pract. 2012;12(5):357–65.
9. McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. Cochrane Database Syst Rev. 2016;(5):CD007126.
10. Pickering G, Moustafa F, Macian N, Dubray C. A new transmucous-buccal formulation of acetaminophen for acute traumatic pain: a non-inferiority, randomized, double-blind, clinical trial. Pain Physician. 2015;18(3):249–57.
11. Alexander L, Hall E, Eriksson L, Rohlin M. The combination of non-selective NSAID 400 mg and paracetamol 1000 mg is more effective than each drug alone for treatment of acute pain. A systematic review. Swed Dent J. 2014;38(1):1–14.
12. Chou R, Deyo R, Friedly J, Skelly A, Weimer M, Fu R, et al. Systemic pharmacologic therapies for low back pain: a systematic review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2017. doi: 10.7326/M16-2458. [Epub ahead of print].
13. Derry S, Wiffen P, Moore R. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database Syst Rev. 2015;(7):CD004768**.**
14. Gillis J, Brogden R. Ketorolac: a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs. 1997;53(1):139–88.
15. Smith L, Carroll D, Edwards J, Moore R, McQuay H. Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. Br J Anaesth. 2000;84(1):48–58.
16. Cassinelli E, Dean C, Garcia R, Furey C, Bohlman H. Ketorolac use for postoperative pain management following lumbar decompression surgery. Spine. 2008;33(12):1313–7.
17. Koh W, Nguyen K, Jahr J. Intravenous non-opioid analgesia for peri- and postoperative pain management: a scientific review of intravenous acetaminophen and ibuprofen. Korean J Anesthesiol. 2015;68(1):3.
18. Pergolizzi J, Taylor R, Raffa R. Intranasal ketorolac as part of a multimodal approach to postoperative pain. Pain Pract. 2014;15(4):378–88.
19. Ketorolac [package insert]. Schaumburg, IL: SAGENT Pharmaceuticals; 2014.
20. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ. 2006;332(7553):1302.

21. Moore R, Derry S, McQuay H. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015;(9):CD008659.
22. Gago Martínez A, Escontrela Rodriguez B, Planas Roca A, Martínez RA. Intravenous ibuprofen for treatment of post-operative pain: a multicenter, double blind, placebo-controlled, randomized clinical trial. PLoS One. 2016;11(5):e0154004.
23. Singla N, Rock A, Pavliv L. A multi-center, randomized, double-blind placebo-controlled trial of intravenous-ibuprofen (IV-ibuprofen) for treatment of pain in post-operative orthopedic adult patients. Pain Med. 2010;11(8):1284–93.
24. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database Syst Rev. 2013;(6):CD010210.
25. Derry S, Moore R. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev. 2013;(10):CD004233.
26. Xylocaine (R), lidocaine [package insert]. Schaumburg, IL: APP Pharmaceuticals, 2010.
27. Marcaine (R), bupivacaine [package insert]. North Chicago, IL: Abbott Laboratories, 1998.
28. Pasero C. Lidocaine patch 5% for acute pain management. J Perianesth Nurs. 2013;28(3):169–73.
29. Bai Y, Miller T, Tan M, Law L, Gan T. Lidocaine patch for acute pain management: a meta-analysis of prospective controlled trials. Curr Med Res Opin. 2015;31(3):575–81.
30. Vrooman B, Kapural L, Sarwar S, Mascha E, Mihaljevic T, Gillinov M, et al. Lidocaine 5% patch for treatment of acute pain after robotic cardiac surgery and prevention of persistent incisional pain: a randomized, placebo-controlled, double-blind trial. Pain Med. 2015;16(8):1610–21.
31. Hu D, Onel E, Singla N, Kramer W, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig. 2012;33(2):109–15.
32. Dumlu E, Tokac M, Ocal H, Durak D, Kara H, Kilic M, et al. Local bupivacaine for postoperative pain management in thyroidectomized patients: a prospective and controlled clinical study. Turk J Surg. 2016;32(3):173–7.
33. Abdolhossein-Davoodabadi, Reza-Fazel M, Reza-Vafaei H, Parviz S. Comparison of the effects of intrapleural bupivacaine and morphine on post-thoracotomy pain. Middle East J Anaesthesiol. 2015;23(3):267–272.
34. Sporer S, Rogers T. Postoperative pain management after primary total knee arthroplasty: the value of liposomal bupivacaine. J Arthroplast. 2016;31(11):2603–7.
35. Yu X, Wang J, Huang L, Yu X, He Z. Efficacy and safety of bupivacaine versus lidocaine in local anaesthesia of the nasopharynx: a meta-analysis. Am J Rhinol Allergy. 2016. [Epub ahead of print].
36. Garg K, Khurana S, Grewal A, Kaul T, Bose A. A comparative study on postoperative pain relief in laparoscopic cholecystectomy: Intraperitoneal bupivacaine versus combination of bupivacaine and buprenorphine. Anesth Essays Res. 2016;10(1):23–8.
37. Nadeau M, Saraswat A, Vasko A, Elliott J, Vasko S. Bupivacaine versus liposomal bupivacaine for postoperative pain control after augmentation mammaplasty: a prospective, randomized, double-blind trial. Aesthet Surg J. 2015;36(2):NP47–52.
38. Knight R, Walker P, Keegan K, Overholser S, Baumgartner T, Ebertowski J, et al. A randomized controlled trial for pain control in laparoscopic urologic surgery: 0.25% bupivacaine versus long-acting liposomal bupivacaine. J Endourol. 2015;29(9):1019–24.
39. Hamilton TW, Strickland LH, Pandit HG. A meta-analysis on the use of gabapentinoids for the treatment of acute postoperative pain following total knee arthroplasty. J Bone Joint Surg Am. 2016;98(16):1340–50.
40. Collins S, Sigtermans MJ, Dahan A, Zuurmond WW, Perez RS. NMDA receptor antagonists for the treatment of neuropathic pain. Pain Med. 2010;11(11):1726–42.
41. Chan AK, Cheung CW, Chong YK. Alpha-2 agonists in acute pain management. Expert Opin Pharmacother. 2010;11(17):2849–68.

42. Honey BL, Benefield RJ, Miller JL, Johnson PN. Alpha-2 receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. Ann Pharmacother. 2009;43:1506–11.
43. Kumar A, Maitra S, Khanna P, Baidya DK. Clonidine for management of chronic pain: a brief review of the current evidences. Saudi J Anasth. 2014;8(1):92–6.
44. Reardon DP, Anger KE, Adams CD, Szumita PM. Role of dexmetomidine in adults in the intensive care unit: an update. Am J Health-Syst Pharm. 2013;70:767–77.

Chapter 17
Hospitalist Management of Injectable Drugs of Abuse

Kevin Conrad and Taylor Austin

Heroin in America Today

Incidence

Heroin use in America is increasing at an alarming rate across all age groups, demographics, and income levels. Some of the greatest increases have occurred in groups with historically low rates of heroin use: women and those with higher incomes. According to national surveillance data, there was a 145% increase in heroin use from 2007 to 2014 and a 286% increase in heroin related deaths from 2002 to 2013 [1, 2]. The prevalence of heroin use is likely even higher than the reported figures because the surveys depend on self-reporting. In 2013, an estimated 4.8 million people in the United States abused heroin at some point in their lives and 289,000 people reported use in the last month [3].

How Did We Get Here?

Heroin (diacetylmorphine) was the trade name of a drug originally developed by Bayer in 1898 as a cough suppressant for people with severe lung disease [4]. Soon after it was introduced, its addictive potential was discovered and by 1920, the Dangerous Drugs Act completely banned the use of heroin for any purpose [5].

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Today, heroin is an illegal opioid drug of abuse that is synthesized from morphine, which is a naturally occurring substance found in the opium poppy plant. Pure heroin, mostly from South America and Southeast Asia, is a white powder with a bitter taste that can be snorted or smoked. Dealers often maximize their profits by mixing additives that produce a variation in colors from white to dark brown powders [5, 6]. "Black tar" heroin is either sticky or hard like coal and is mostly produced in Mexico. The black color is due to crude processing methods that leave many impurities. This type of heroin is usually dissolved and injected into veins, muscles, or under the skin [6].

Historically, heroin users tended to be young men in their mid-teens, whose first opioid drug exposure was heroin. Whites and ethnic groups had equal proportions of use. This demographic has dramatically shifted with the rise in current new users more likely to be white, to be older, to live in nonurban areas, and to have previously abused prescription opioids. Interestingly, some of the greatest increases in use have been seen in female and middle-class populations [7].

The resurgence of heroin use can be blamed in part by the increase of opioid prescriptions. In the 1990s, physicians were encouraged to increase the use of pain medications, leading to non-therapeutic opioid prescriptions for white, middle class, nonurban patients who frequented the doctor. For those who became addicted to prescription opioid drugs, heroin was often cheaper and easier to obtain. Heroin is also usually stronger and easier to use intravenously; opioid pills are more difficult to convert into an injectable solution [7].

Initiating Recovery: The Hospitalists Role

Using the Biopsychosocial Model for the Treatment of Addiction

Recovery and treatment can and should begin during a Hospitalization. This can be seen a learning moment and an opportunity to initiate a lengthy process. Resources are often limited as many patients are often underinsured. It may be beneficial to develop partnerships with community clinics. Within an individual group a leader may be selected to lead this initiative. It is important to understand the basic tenets and barriers in treating addiction.

The American Psychiatric Association stresses that psychosocial treatments are essential in treating opioid use disorder. They recommend community reinforcement approach whereby patients find activities in their environment that are pleasurable when sober. It encourages rewarding community involvement and family or friend involvement as positive reinforcement [8]. While a patient is going through treatment with medically assisted recovery, the concept of "recovery capital" is an important predictor of success in quitting. Recovery capital includes personal biopsychosocial resources that patient can use during their recovery journey such as: stable and supportive relationships (social capital), suitable housing (physical capital), skills, physical and mental health, employment (human capital), and constructive values, beliefs, and attitudes (cultural capital) [9, 10].

Despite guidelines and recommended treatment strategies that exist, political barriers still remain. Only approximately 21% of patients with opioid dependence are treated in the United States, compared to 50% in Europe. Some of these barriers include cost of maintenance treatment, lack of availability in many areas, and insurance coverage [11].

Homelessness

Success in treating the homeless population has been demonstrated with Standard Case Management (SCM). SCM is led by a case manager that focuses on the coordination of services for homeless patients. The only systematic review to analyze different models of case management in homeless populations concluded that SCM is the most effective case management model for homeless people with substance use disorder over other models of case management like intensive case management, assertive community treatment, and critical time interventions. SCM in this population has also been shown to be significantly more effective than referral to community services in reducing alcohol and drug use in homeless substance users [12].

Behavioral Contracts

Behavioral contracts, also known as contingency management, are tools where the patient is incentivized to maintain a sober lifestyle. Patients receive incentives or rewards for meeting specific behavioral goals (such as verified abstinence), and this method of achieving sobriety has consistently proven effective in managing substance use with current and prior reviews reporting an 86 and 88% efficacy rate, respectively [13]. This empirical support has led to the adoption of behavioral contracts for intensive outpatient treatment for illicit drug disorders within the US Veteran Administration hospital system [14]. For opioid-dependent populations, behavioral contracts are used specifically in some methadone clinics; the patient is allowed to have their methadone dose only if their urine sample is drug-free [13].

Psychiatric Management

Up to 30% of intravenous drug abusers have a psychiatric co-morbidity [15]. People with psychiatric disorders are also more likely to use drugs as a method of self-medication. Psychiatric disorders can complicate treatment and create risk of relapse; therefore, appropriate psychiatric management is warranted. Patients admitted to the hospital should be screened with a detailed mental status examination prior to and after beginning agonist or antagonist treatment. Suicidal ideation and behavior should always be screened for, as actively suicidal patients are not good candidates for any opioid treatment [16].

Inpatient Management of Withdrawal

Heroin withdrawal usually occurs within 12 h of the last use, peaks at 24–48 h, and subsides over 3–5 days. Symptoms of withdrawal are not usually life threatening and include muscle aches, increased tearing, runny nose, dilated pupils, piloerection, agitation, anxiety, insomnia, sweating, yawning, abdominal cramping, nausea, vomiting, diarrhea. Precipitated withdrawal, whereby the administration of an opioid antagonist such as naloxone or a partial antagonist like buprenorphine displaces the agonist opioid from the mu receptor, can be more severe [16]. A baseline assessment of opioid withdrawal should be measured with a standardized tool such as the Clinical Opioid Withdrawal Scale (COWS) (Fig. 17.1).

Management of opioid withdrawal can be completed in both outpatient and inpatient settings. Although there is a lack of evidence that inpatient management is safer, inpatient treatment has higher rates of completion. It is recommended that pregnant women do not undergo opioid withdrawal and instead begin a methadone maintenance treatment as withdrawal can induce miscarriage or premature labor. It is difficult to assess whether the opioid withdrawal, opioid use, or co-occurring use of other drugs contributes to the obstetrical complications associated with opioid use in pregnancy such as preeclampsia, miscarriage, premature delivery, fetal growth restriction, and fetal death [16].

There are two main strategies in treatment of opioid withdrawal. The first strategy includes providing gradually tapered doses of opioid agonists such as methadone or buprenorphine. This has been proven to be more effective in patient retention and abstinence. Methadone tapers of 20–30 mg per day generally are completed in 6–10 days. Buprenorphine is not specifically US FDA-approved for withdrawal management but is still widely used for this indication. Since buprenorphine is a partial opioid antagonist, it is important not to begin this medication until the patient begins experiencing opioid withdrawal to avoid precipitated withdrawal. Buprenorphine is started at 4–16 mg per day, and tapers can be brief (3 days) or as long as 30 days or more as guided by patient response [16]. A recent *Cochrane* review found that at fixed medium or high doses, buprenorphine and methadone have no difference in treatment retention but at flexible doses, which is usually standard in patient care, methadone retains more patients [17].

The concern for methadone dependence, the long methadone withdrawal course, and government restrictions on methadone prescriptions led to the use of clonidine as a way to reduce symptoms of withdrawal [18]. Clonidine, an alpha-2 adrenergic agonist, acts centrally to decrease noradrenergic hyperactivity.

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

<table>
<tr><td colspan="2">Patient's Name:_____ Date and Time
____/_____/____:_____

Reason for this assessment_____</td></tr>
<tr><td>Resting Pulse Rate:
_____beats/minute
Measured after patient is sitting or lying for one minute

0 pulse rate 80 or below

1 pulse rate 81–100
2 pulse rate 101–120
4 pulse rate greater than 120</td><td>GI Upset: over last ½ hour
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 Multiple episodes of diarrhea or vomiting</td></tr>
<tr><td>Sweating: over past ½ hour not accounted for by room temperature or patient activity.
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face</td><td>Tremor observation of outstretched hands
0 No tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching</td></tr>
<tr><td>Restlessness Observation during assessment
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms</td><td>Yawning Observation during assessment
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment</td></tr>
</table>

Fig. 17.1 The clinical opioid withdrawal scale (COWS). California Society of Addiction Medicine. 2008. Guidelines for Physicians Working in California Opioid Treatment Programs. Score: 5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

5 Unable to sit still for more than a few seconds	4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment: _____

Fig. 17.1 (continued)

Clonidine can be given at doses 0.1–0.3 mg every 6–8 h, with a maximum dose of 1.2 mg daily. Patients must be monitored for hypotension. Adjunctive medications used to treat symptoms include benzodiazepines for anxiety, loperamide or bismuth-salicylate for diarrhea, acetaminophen or NSAIDs for pain, and ondansetron for nausea [16]. Guanfacine and lofexidine are medications similar to clonidine, which are off-label alternative with fewer side effects. There is enough evidence to support that clonidine is more effective than placebo in managing withdrawal from heroin. When compared to methadone treatment, clonidine has more hypotensive or adverse effects but the duration of treatment is significantly shorter than methadone tapers. There is not enough evidence to compare overall effectiveness of reducing doses of methadone with alpha-2 adrenergic agonists [18].

Anesthesia-assisted opioid withdrawal using large doses of naloxone to precipitate withdrawal under anesthesia is no longer recommended due to the high potential for severe pulmonary edema and cardiac arrest and death [19].

Hospital Violence

Violence Against Healthcare Providers

Disruptive behavior is common during withdrawal from opioids. Aggression and/or violence can stem from delirium, anxiety, or anger about being in a closed setting without access to usual amounts of narcotics. Many of these patients have comorbid psychiatric disease that impairs their insight and judgment.

Hospital violence against healthcare providers is a real issue that is underreported, persistent, and pervasive. Nurses have the highest rates of verbal and physical assaults, but only 30% report incidents of workplace violence for fear of retribution from supervisors, legal involvement, and complacency of violence as a normal occurrence within the hospital [20]. From 1993 through 2001, violence against physicians occurred at a rate of 10.1 per 1000 workers [21]. In one study, 89% of assaults against physicians were carried out by patients, 9% by patient's family members, and 2% by patients' friends [22]. Rates of workplace violence against physicians is highest in psychiatric settings with one review showing that the annual incidence of verbal conflict in a psychiatric hospital was 99% and physical assault was 70% [23].

Violence due to the opioid epidemic is now one of the top three security issues facing many hospitals in America [24]. It has been a challenge to develop systems that respect the vulnerability of these patients but at the same time provides safety for the providers. A visibly increased security presence at all levels from admission to the medical unit to discharge has been advocated as a means to improve hospital security. Dedicated chemical dependency wards, de-escalation programs, and ongoing staff training at larger hospitals have also been utilized [24].

Drug Dealing in the Hospital

The use of heroin within the hospital is also a rising problem for hospitalists. There has been a rise in heroin users admitted to hospital medicine services, who then proceed to inject drugs during their stay. Also, drug dealing within the hospital setting is becoming more common, as drug dealers enter the hospital to supply illicit substances to patients [25]. This is a serious security issue, as it is difficult for staff to recognize who friends and family are versus who enters to deal. The issue of patient confidentiality also arises, if the decision is made to report the drug dealer to police. Hospital medicine in conjunction with nursing, local law enforcement and hospital security and legal representatives should formalize plans to deal with this issue. This may include security rounds,

dedicated units, and visitor screening. The need for providing a healing environment in the hospital should not prevent proper security measures to be undertaken.

Infections

Local Infections

Skin and soft-tissue infections are common and are usually caused by the patient's commensal flora. Risk factors for local infections include using dirty needles, failing to clean the skin before injection, being positive for HIV, "booting" (repeatedly flushing and pulling back during injection), and using saliva. Heroin users have reported chewing up tablets to form a solution to inject, or even licking the needle before injection. Some users who lack viable veins resort to "skin popping" (subcutaneous or intramuscular injection), which is associated with higher rates of soft-tissue infection than intravenous drug use alone. Organisms responsible for bacterial infections in drug users include *Staphylococcus aureus* (including community-associated MRSA, Streptococcus species, groups A, C, and G; *Streptococcus anginosus*, *Pseudomonas aeruginosa*, gram-negative bacteria, oral anaerobes, and *Mycobacterium tuberculosis*.

Abscesses in this patient population have been mistaken for spider bites. Community-associated MRSA should be considered in a patient with a history of injection drug use and abscesses, especially if they are complicated. Osteomyelitis in uncommon places such as sternoclavicular and sacroiliac joints can be caused by injecting into the jugular vein or femoral vein. Such infections can be polymicrobial or anaerobic, especially if saliva contaminated the drug equipment. Femoral vein injection specifically increases the risk for gram-negative flora complications.

Clostridial infections are uniquely associated with black-tar heroin use. Injection of black-tar heroin into the soft tissues causes necrosis, which creates an anaerobic environment where clostridial microbes flourish. In these patients, tetanus immunization status should be determined. Toxin-mediated disease such as botulism can present with slurred speech and can be mistaken for intoxication [26]. IV drug use is now the most common etiology for botulism in the UK with steady diagnosis rate increases seen in America as well [27, 28].

Spinal Cord Infections

Spinal epidural abscesses occur in heroin users when bacteria are usually seeded hematogenously from unsterile injection technique or by soft-tissue infections. The location of the spinal abscess may correlate with the location of drug injection, with cervical and lumbar spine more likely to be affected by upper and lower extremity locations of injection, respectively. Among IV drug users, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common pathogens.

A high degree of suspicion for a spinal abscess is needed as fever is only found in 50% of patients and back tenderness is not always present. Other manifestations

of epidural abscesses include motor weakness, radiculopathy, bladder and bowel dysfunction, and atypical signs such as sudden paralysis, abdominal pain, and headache can also be present [29]. The average time to diagnosis is a month but can take up to six months in some cases, hindering effective management and treatment [30]. As the prognosis depends on the timeliness of its diagnosis, many heroin abusers are at substantial risk of neurological deficits or death due to avoidance or delay of medical care.

Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are almost always elevated and leukocytosis is reported in 60–80% of patients. Blood cultures should be obtained to determine antibiotic sensitivities but usually only reveal an organism in 50% of cases. MRI has a greater than 90% sensitivity and specificity for localizing the abscess. If MRI is positive, biopsy should be performed to direct antibiotic management [29]. Surgery should be considered in patients with significant bone involvement, neurological deficits, sepsis with clinical toxicity unresponsive to antibiotics, failure of needle biopsy to obtain needed cultures, and failure of IV antibiotics to eradicate the infection [30].

Patients with spinal abscesses with overt neurological complications tend to do poorly. In one study, patients with preoperative neurological defects present less than 36 h showed some improvement, whereas the majority of patients with deficits present more than 36 h did not show improvement [31]. Patients with full paralysis greater than 36 h often died [32].

Endocarditis

The overall incidence of bacterial endocarditis among injection drug users (IDUs) is about 1.5–20 per 1000 users per year. Right-sided infectious endocarditis (IE) occurs up to 76% in IDUs compared with just 9% in non-users. The mortality rate of right-sided endocarditis is lower than left sided, however the morbidity associated with right-sided disease is greater due to ophthalmologic, cardiopulmonary, neurologic, renal, and extremity vascular complications. It is hypothesized that the increased prevalence of right-sided endocarditis is due to multiple factors such as the toxic effect of injected substances, the differences in valves and valvular epithelium in IDUs, the infecting organisms and bacterial load, and immunologic changes in IDUs. The most commonly isolated pathogens found in right-side endocarditis is *Staphylococcus aureus* and *Pseudomonas aeruginosa* [33].

Diagnosis of IE in IDUs can be difficult because acute endocarditis usually evolves too quickly for the development of immunological vascular phenomena such as Osler nodes and Roth spots, which are more characteristic of the later stages of the disease when physical exam findings can be appreciated. Also, left sided lesions are more likely to produce peripheral emboli. The modified Duke criteria is the most widely used and most current tool to diagnose infective endocarditis (Fig. 17.2). If IE is suspected, at least three sets of blood cultures obtained from different venipuncture sites should be drawn with the first and last samples drawn at least 1 h apart. Echocardiography should be performed immediately [34].

Definitive infective endocarditis

Pathologic criteria

1. Microorganism detected by culture or histology of a vegetation or intracardiac abscess OR
2. Pathologic lesions such as vegetation or intracardiac abscess confirmed by histological examination

Clinical Criteria

1. 2 major clinical criteria OR
2. 1 major and 3 minor clinical criteria OR
3. 5 minor clinical criteria

Possible infective endocarditis

1. 1 major and 1 minor clinical criteria OR
2. 3 minor clinical criteria

Rejected infective endocarditis

1. A firm alternative diagnosis OR
2. Resolution of clinical manifestations with antibiotic therapy for ≤4 days OR
3. No pathological evidence of infective endocarditis at surgery or autopsy with antibiotic therapy for ≤4 days

Major clinical criteria

Positive blood cultures for infective endocarditis (one of the following):

Typical microorganisms from two separate blood cultures

1. Staphylococcus aureus
2. Viridans streptococci
3. Streptococcus gallolyticus (formerly S. bovis)
4. Community acquired enterococci in the absence of a primary focus HACEK group OR

Persistently positive blood culture

For organisms that are commonly skin flora: 3 or a majority of 4 or more separate blood cultures (with first and last drawn at least one hour apart

Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer >1:800

Evidence of endocardial involvement (one of the following):

Echocardiogram:

1. vegetation OR
2. abscess OR
3. new partial dehiscence of prosthetic valve

New valvular regurgitation

Minor clinical criteria

1. Predisposition: predisposing heart condition or injection drug use
2. Fever greater than 38.0 C
3. Vascular phenomena: arterial emboli, intracranial hemorrhage, Janeway lesions, conjunctival hemorrhage, septic pulmonary infarcts, mycotic aneurysm
4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Roth spots, Osler nodes
5. Microbiological evidence: positive blood culture but not meeting major criterion or endocarditis

Fig. 17.2 The modified Duke criteria for diagnosing infective endocarditis. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000. 30(4):633–8

The Infectious Disease Society recommends treating uncomplicated MSSA-positive right-sided IE with either parenteral β-lactam or daptomycin short-course therapy of two weeks. The standard approach for treatment of right-sided IE used to be nafcillin or oxacillin plus gentamycin, however, current evidence demonstrates that adjunctive aminoglycoside therapy is unnecessary and causes renal toxicity. MRSA-positive right-sided IE usually requires a longer treatment regime with a glycopeptide such as teicoplanin or vancomycin. Infectious disease subspecialists should be consulted in all IDU infectious endocarditis cases in order to create an optimal empirical treatment regimen at the time of initiation of antibiotic therapy.

Surgical intervention with valve prosthesis should be avoided if possible due to the subsequent risk of device infection with continued drug use. Surgery is warranted if the patient develops right heart failure secondary to severe tricuspid regurgitation, sustained infection with difficult-to-treat organisms, tricuspid valve vegetations larger than 20 mm in diameter and recurrent pulmonary embolism despite antibiotic therapy, or lack of response to appropriate medical therapy [34].

Long-Term Antibiotic Management

Risk of at Home Treatment

Patients with osteomyelitis, endocarditis, and some skin/wound infections might need to be discharged on outpatient parenteral antimicrobial therapy (OPAT) [35]. OPAT can be delivered by four basic models: by a physician or other health care professional at an infusion center, by a visiting nurse or health care professional at home, by self- or caretaker-administration at home, or in a skilled nursing facility or long-term acute care hospital. Vascular access is chosen based on the diagnosis, antimicrobials prescribed, frequency of administration, the need for a programmable infusion pump, and the anticipated duration of therapy [36]. The use of OPAT in IV drug users is controversial because physicians are hesitant to prescribe a device that could be abused and therefore create more harm [37]. There are no established guidelines on long-term antibiotic use in this patient population [35]. In selected individual cases OPAT has been considered with the use of patient contracts, tamper-proof security seals, and at home drug testing [37].

Oral Alternatives

Some small studies have shown that a short course (four-week) of oral ciprofloxacin plus rifampin can be effectively used as an alternative to an OPAT if the patient has tricuspid valve involvement only, the infection has in vitro susceptibility to oral agents, and long-term intravenous therapy is difficult or impossible [34, 38, 39].

However, short-course intravenous or oral antibiotics are not appropriate for aortic or mitral valve involvement, MRSA, or complications such as heart failure or perivalvular abscesses. If a patient needs to be discharged on oral medications, a higher rate of adherence will most likely occur if the patient is participating in a structured opioid maintenance program [40].

References

1. Today's Heroin Epidemic. 2015, July 07. Retrieved February 01, 2017, from http://www.cdc.gov/vitalsigns/heroin.
2. Compton W, Jones C, Baldwin G. Relationship between nonmedical prescription-opioid use and heroin use. N Engl J Med. 2016;374:154–63.
3. National Survey on Drug Use and Health: Detailed Tables. Center for Behavioral Health Statistics and Quality; Substance Abuse and Mental Health Administration, MD; 2014.
4. Sneader W. The discovery of heroin. Lancet. 1988;325:1697–9.
5. Habal T. Heroin toxicity. 2016. Retrieved January 27, 2017, from http://emedicine.medscape.com/article/166464-overview#a4.
6. National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. Retrieved January 22, 2017, from https://www.drugabuse.gov/publications/drugfacts/heroin.
7. Kuehn B. Driven by prescription drug abuse, heroin use increases among suburban and rural whites. JAMA. 2014;312(2):118–9.
8. American Psychiatric Association. Practice guideline for the treatment of patients with substance use disorders, 2nd ed. 2006. Available at: http://www.psych.org. Accessed 29 Jan 2017.
9. Parmenter J, Mitchell C, Keen J, Oliver P, Rowse G, Neligan I, Keil C, Mathers N. Predicting biopsychosocial outcomes for heroin users in primary care treatment: a prospective longitudinal cohort study. Br J Gen Pract. 2013;63(612):e499–505. doi:10.3399/bjgp13X669220.
10. Schottenfeld R, O'Malley S. Meeting the growing need for heroin addiction treatment. JAMA Psychiatry. 2016;73(5):437–8.
11. Fischer PJ, Breakey WR. The epidemiology of alcohol, drug, and mental disorders among homeless persons. Am Psychol. 1991;46(11):1115–28.
12. de Vet R, van Luijtelaar M, et al. Effectiveness of case management for homeless persons: a systematic review. Am J Public Health. 2013;103(10):e13–26.
13. Davis D, Kurti A, Skelly J, Redner R, et al. A review of the literature on contingency management in the treatment of substance use disorders, 2009–2014. Prev Med. 2016;92:36–46.
14. Petry N, DePhillips D, Rash C, Drapkin M, McKay J. Nationwide dissemination of contingency management: the Veterans Administration initiative. Am J Addict. 2014;23(3):205–10.
15. Dausey DJ, Desai RA. Psychiatric comorbidity and the prevalence of HIV infection in a sample of patients in treatment for substance abuse. J Nerv Ment Dis. 2003;191(1):10–7.
16. The ASAM. National practice guideline: for the use of medications in the treatment of addiction involving opioid use. Am Soc Addict Med. 2015:32–5.
17. Mattick R, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review). Cochrane Database Syst Rev. 2014;2(2):1–54. doi:1002/14651858.
18. Gowing L, Farrel M, Ali R, White J. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2016;5(3). doi:10.1002/14651858.
19. Nicholls L, Bragaw L, Ruetsch C. Opioid dependence treatment and guidelines. J Manag Care Pharm. 2010;16(1-b):S14–21.

20. Phillips J. Workplace violence against health care workers in the United States. N Engl J Med. 2016;374:1661–9.
21. Perkins CA. Weapon use and violent crime: National Crime Victimization Survey 1993–2001. Washington, DC: Department of Justice, Office of Justice Programs, Bureau of Justice Statistics; 2003.
22. Kowalenko T, Walters BL, Khare RK, Compton S. Workplace violence: a survey of emergency physicians in the state of Michigan. Ann Emerg Med. 2005;46:142–7.
23. Kelly EL, Subica AM, Fulginiti A, Brekke JS, Novaco RW. A cross-sectional survey of factors related to inpatient assault of staff in a forensic psychiatric hospital. J Adv Nurs. 2015;71:1110–22.
24. Burmahl B, Morgan J. Hoppszallern S. Hospital security plans stress prevention. Hosp Secur Surv. 2016. Accessed from: http://www.hfmmagazine.com/articles/2431-hospital-security-survey. Accessed 13 Feb 2017.
25. Kennedy R. 20 Arrested in drug dealing in a Brooklyn V.A. hospital. 1995. The New York Times. Available from: http://www.nytimes.com/1995/09/14/nyregion/20-arrested-in-drug-dealing-in-a-brooklyn-va-hospital.html. Accessed 10 Feb 2017.
26. Gordon R, Lowy F. Bacterial infections in drug users. N Engl J Med. 2005;353:1945–54.
27. Vera J, Hensiek A, Woodrow C, Crawley F, Krishna S. Ophthalmoplegia and slurred speech in an intravenous drug user. PLoS Med. 2006;3(12):e453.
28. Yuan J, Inami G, Mohle-Boetani J, Vugia D. Recurrent wound botulism among injection drug users in California. Clin Infect Dis. 2011;52(7):862–6.
29. Bond A, Manian F. Spinal epidural abscess: a review with special emphasis on earlier diagnosis. Biomed Res Int. 2016;2016:1614328.
30. American association of neurological surgeons. Spinal Infections. 2016. Accessed from: http://www.aans.org/Patient%20Information/Conditions%20and%20Treatments/Spinal%20Infections.aspx. Accessed 12 Feb 2017.
31. Danner RL, Hartman BJ. Update of spinal epidrual abscesses: 35 cases and review of the literature. Rev Infect Dis. 9:265–74.
32. Maslen DR, Jones SR, Crisplin MA, et al. Spinal epidural abscess: optimizing patient care. Arch Intern Med. 153:1713–21.
33. Frontera J, Gradon J. Right-side endocarditis in injection drug users: review of proposed mechanisms of pathogenesis. Clin Infect Dis. 2000;30:374–9.
34. Baddour LM, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435–86.
35. Papalekas E, Patel N, Neph A, Moreno D, Zervos M, Reyes K. Outpatient parenteral antimicrobial therapy (OPAT) in intravenous drug users (IVDUs): epidemiology and outcomes. Open Forum Infect Dis. 2014;1(Suppl 1):S52–3.
36. Paladino J, Poretz D. Outpatient parenteral antimicrobial therapy today. Clin Infect Dis. 2010;51:S198–208.
37. Ho J, Archuleta S, Sulaiman Z, Fisher D. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. J Antimicrob Chemother. 2010;65(12):2641–4.
38. Sexton D, Chu V. Infective endocarditis in injection drug users. 2016. Retrieved January 29, 2017 from http://www.uptodate.com/contents/infective-endocarditis-in-injection-drug-users.
39. Torres-Tortosa M, de Cueto M, Vergara A, Sánchez-Porto A, Pérez-Guzmán E, González-Serrano M, Canueto J. Prospective evaluation of a two-week course of intravenous antibiotics in intravenous drug addicts with infective endocarditis. Grupo de Estudio de Enfermedades Infecciosas de la Provincia de Cádiz. Eur J Clin Microbiol Infect Dis. 1994;13(7):559.
40. Mertz D, Viktorin N, Wolbers M, Laifer G, Leimenstoll B, Fluckiger U, Battegay M. Appropriateness of antibiotic treatment in intravenous drug users, a retrospective analysis. BMC Infect Dis. 2008;8:42.

Part IV
Perspectives in Hospital Medicine

1.1 Introduction

After rapid growth, hospital medicine in some ways will need to redefine itself. The trends in hospital medicine will provide a snapshot of where we currently are. It is essential that all have this knowledge as we discuss and implement the future of the specialty.

Hospital medicine is growing as a specialty on a global level, with each country experiencing unique growing pains. Comparing the various systems provides insight to our own development and at the same time fosters collaboration. The international chapter provides unique insights into hospital medicine from around the world. An interesting contrast is seen between systems depending on the financial funding in each country.

Lastly, it is impossible to practice Hospital medicine without exploring the topics of philosophy practice. Despite our ever-increasing attachment to electronic medical records and algorithmic driven practice patterns, hospital medicine remains closely entwined with the basic philosophical questions that life and death poses. The last chapter attempts to provide basic philosophical tools that we can use in our daily practice. The practice of hospital medicine can be emotionally difficult. Dealing with fragility, drug abuse and death on a daily basis can take its toll. Philosophical tools may assist in dealing with that burden.

Chapter 18
The Current State of Hospital Medicine: Trends in Compensation, Practice Patterns, Advanced Practice Providers, Malpractice, and Career Satisfaction

Kevin Conrad and Theodora Valovska

Size and Growth

Hospital medicine is approximately 20 years old. The term Hospitalist was first utilized in a 1996 New England Journal of Medicine article written by Goldman and Wachter [1]. It has been the fastest growing specialty in the history of medicine. The scope of hospital medicine continues to focus on acute patient care, teaching, research, and leadership related to the delivery of hospital-based care. The emergence of hospital medicine in the United States has both similarities with and differences from acute medicine practiced in other countries, reflecting health system differences.

Although common in other countries, before 1996, there were limited physician practices based solely in the hospital. Several forces, primarily financial, aligned in the 1990s to account for the birth and strong growth of the specialty. A shift away from fee for service made a hospital admission an expensive cost that needed to be managed in a timely and quality driven manner. The clinic-based physician neither had the time nor the expertise to efficiently deal with an in patient practice. Out of these circumstances rose the specialty of hospital medicine.

Currently, there are 50,000 practicing Hospitalists in the United Sates. This represents a steady and slightly exponential growth of roughly 2850 new Hospitalist per year for the past 15 years [2]. This expansion is predicted to continue for the next few years as remaining hospitals develop new hospitalist's programs, and the scope of practice continues to expand. It is larger than any other subspecialty of Internal

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Medicine with Cardiology at 22,000 being the closest. Approximately 75% of all Hospitals in the U.S. employ hospitalists, with the percentage increasing yearly.

Hospitalists Metrics: Increasing Analysis

Initially, there were fragmented and limited statistics to define the specialties' growth and performance. Individual programs evolved with little guidance, other than inferring from the practice guidelines of clinic-based and emergency room physicians. Before 10 years ago hospitalists reports were often not separated from clinic-based Internal Medicine physicians in the development of performance studies. Over the past 5 years, several firms including Truven, The Medical Group Management Association (MGMA), and the Society of Hospital Medicine (SHM) have developed extensive reviews of compensation, practice patterns, and overall trends for hospitalists. With 50,000 practitioners, hospital medicine has expectedly become a closely followed specialty.

One of the leaders in producing hospital medicine surveys has been the Society of Hospital Medicine (SHM). SHM founded in 1997 has had exponential growth like the specialty. It publishes the only peer review journal on Hospital Medicine in the United States. SHM in conjunction with the Medical Group Management Association (MGMA) produces the most comprehensive annual report on the State of Hospital Medicine. Its validity is derived from the most extensive yearly survey taken of providers and practice leaders [2].

Compensation

According to the Society of Hospital Medicines 2016 report, the mean salary for hospitalists serving adult patients was $297,104. This represents a continued overall increase in salaries over the past 15 years and a 9.6% increase from 2014. Since 2010 there has been on average a 9% increase in salary each year [2]. Compensation growth is expected to continue to be strong in the near future as hospitalists positions continue to outnumber graduating housestaff and competition remains in filling positions.

The median salary was $278,471, which represents some high earning outliers as well as the pay differential for nocturnists. There continues to be variation by geographic region with the highest mean salary occurring in the South being $333,352. Hospitalists working in physician-owned practices have had larger compensation increases than those in hospital-owned groups, according to the MGMA Provider Compensation 2016 report [3].

Some other trends emerge from a survey taken in 2016 in Today's Hospitalist magazine. More than 8% earn over $400,000. This is usually accomplished by working shifts beyond the typical model or in a geographically isolated area. Also noted in this report was a direct correlation between years worked and an

increased salary with those working greater than 10 years earning an average of $294,682 [4].

Among internists and family physicians, more hospitalists (39% each) reported receiving an increase in their salary vs. their non-hospitalist peers (33 and 37%, respectively) in the past year [3, 4, 5].

The median leadership stipend for all sized groups was 14%. The median pay differential for nocturnists was 15% which has increased from 10% in 2014 [2]. This may represent that the majority of programs have recently developed in-house nocturnist coverage, increasing demand for this practice pattern.

Hospitals continue to provide financial support for programs. Over 90% of programs do not receive enough income alone from professional fees to cover expenses of running the group. The median support per FTE was 157,535 in 2016 [2].

Performance Metrics

The amount of hospitalist compensation tied to performance metrics continues to increase, with currently 80% being base pay and approximately 15% being production and 5% performance metrics [2].

The three most commonly used metrics are patient satisfaction, core measure performance, and readmission rates. Many organizations have recently linked hospitalist compensation to outcomes including mortality and morbidity, while others are continuing to use performance metrics related to the average length of stay, early morning discharge orders, and ED response time.

Since 2014 core measures and documentation are declining as a metric. It is anticipated that the use of performance metrics tied to compensation will continue to increase as the transition to value-based purchasing continues. There continues to be discussions on the efficacy of performance metrics and their impact on morale. Some have argued that incentivizing expected activities does little to improve outcomes and increases burnout. The correct mixture and application of performance metrics will continue to evolve.

Metrics: Changing Patterns

In increasingly capitated systems focused on population health, metrics will continue to shift form revenue generation to measures that look at efficiency and performance. This will emphasize value over volume and quality over quantity [6]. Although still a common metric, Relative Value Units will be used less often as a metric. There will be an increased emphasis on reducing costs. New metrics such as costs per discharge are being implemented. These calculations are more time consuming but are argued to reflect more accurately the value hospitalist bring to the hospital system [6]. In general, future metrics will reflect the fact that a hospitalist can save more money than he or she can generate.

Benefits

The median benefits per provider was $30,000. The median dollars provided for Continuing Medical Education (CME) in 2016 was $4000. Over tha past ten years, there has been little change in the the funding for both CME and benefits [2].

Hospitalists at physician-owned practices had twice the benefits as those in hospital employed groups. Analysts suggest that this is due to physician-owned practices optimizing their retirement contributions for doctors, unlike hospital groups which have to provide a uniform benefits practice to all employees.

There are some differences in paid time off between academic and nonacademic programs. Hospitalists working at teaching hospitals received paid time off 50% of the time. Nonteaching hospitalists have paid time off 22.7% of the time. It is expected in many employment models that all time off will be incorporated into days not worked.

Advanced Practice Providers (APPs)

Nurse Practitioners (NP) and Physician Assistants (PA)

There continues to be rapid growth in the use of advanced practice providers (APP). The number of PA in the United States has increased 36.4% over the last 5 years. The growth of NPs has been even greater with their numbers doubling in the past decade [2]. The 2012 State of Hospital Medicine report revealed that a slight majority of 51.7% of hospital medicine groups employed nurse practitioners (NP) and physician assistants (PA) in their practice. 2 years later, the survey showed 83% of hospital medicine groups reported having NP and PA in their practice [2].

Mean compensation in 2016 was $105,149 for NP and PA. Mean collection for professional charges for NP and PA is $60,198 as compared to $222,651 for physician hospitalists. The collection number may not reflect the overall productivity of APPs as practice models do always allow for billing by midlevel providers.

Limited data exists concerning patient satisfaction, length of stay, overall morbidity, and other quality metrics. In general, all initial data concerning the performance of APP has been positive [7]. Extensive studies that have looked at quality metrics are over a decade old and do not reflect the new expanded roles that APPs have undertaken.

The mean turnover rate per year for PA and NP is 7.3% as compared to 6.9% for physician hospitalists. The increased turnover rate can be attributed to several factors including high demand, the ability to work in a variety of practice settings, and demographics of APPs [2].

The impact of APPs on malpractice claims is uncertain as data is limited. The most comprehensive study of malpractice claims against NPs and PA was published in 2009. It analyzed claims filed between 1991 and 2007 and was recorded in the National Practitioner Data Bank. The study documented one malpractice payment

for every 2.7 active physicians, one malpractice payment for every 32.5 active physician assistants, and one payment for every 65.8 NPs. In the study, 37% of physicians, 3.1% of PAs, and 1.5% of NPs had to make a malpractice payment over the course of the study [8]. Since that time APP have become more independently functioning in hospital services and liability is expected to increase. So far an increase in liability has not been reported, but this is being closely followed.

Between 2003 and 2013, only 2791 malpractice judgments were returned against NPs in the United States. According to data compiled by The Doctors Company on claims that had been awarded, most malpractice claims primarily attributed to APPs can be traced to clinical decision making. The second most common was the lack of specific written protocols concerning supervision. Insufficient training during orientation was also noted [9].

Practice Patterns: Schedules

38% of groups have a 7-day-on 7-day-off schedule. 12-h shifts are the usual norm within this block system. The seven on/seven off schedule becomes more prominent as group size increases. In the past several years, many scheduling models have been instituted with varying degrees of success and acceptance. In the past 5 years, the week on week off model or some variant of that has become the most common schedule. This has had the benefit of simplifying scheduling for many groups [2].

The long-term benefits of a 7-day-on and 7-day-off schedule have recently been challenged by hospitalist leaders nationwide. Bob Wachter, MD, one of the original founders of hospital medicine, weighed in on the 7-day-on 7-day-off schedule at the Society of Hospital Medicine 2016 Annual Meeting stating [10], "It was a mistake, At the time the schedule was designed, nearly every hospitalist was 30 to 40 years old. However, the demographics have changed," Dr. Wachter has pointed out. "I believe the 7-day-on, 7-day-off schedule is the schedule you would create for a 30-year-old finishing residency taking his or her first job." Others have noted that block scheduling limits interaction of hospitalists with important administrative duties within the hospital, and may be factor in burnout as it has been reported to be with emergency medicine.

In response to this, variable schedules among hospitalist within the group have become more common. The variability is particularly seen among the larger groups. 30.9% of all groups had some part of the practice employing a Monday through Friday schedule with weekend coverage.

The mean covered shift per year among all groups was 183, which has been stable over the past several years.

84% of groups had a nocturnist on site, with advanced practice providers increasingly being utilized, either alone or in conjunction with a physician.

The median work relative value units (wRVUs) was 4254. This has remained relatively steady over the past few years. Mean gross charges per year were $425,249, down from $437,692 in 2014 despite stable wRVUs.

There is variable data as to the average daily census of an individual hospitalist, with ranges from 11.8 to 15 patient encounters per day being reported. An interesting study published in the Journal of American Medicine reported that the maximum number of patients a hospitalist can efficiently manage is approximately 15. After that, length of stay and quality metrics decline [11]. This continues to be a subject of discussion among hospitalist groups. Programs vary markedly in the acuity of their patients, but a patient census of 15 has become the standard starting point involving discussion of optimum patient volumes.

Forty-three percent of hospitalists spend 30–45 h per week seeing patients, and 47% spend more than that. According to a government analysis, middle-aged physicians among all specialties work harder than both their younger and older peers [8]. Working hours peak between the ages 46 and 55. Younger doctors (36–45) work fewer hours than previous generations, possible due to lifestyle choices by those in those age groups. Many in this age group are working part time [12].

Scope of Practice

Hospitalists groups continue to offer services outside the traditional practice range of Internal Medicine. There has been a decline however on groups that are willing to provide extensive services. This has included in the past, obstetrical, neurosurgical, and general surgery admissions. Only 14% would define themselves as providing a full range of services as opposed to 67% in 2010. After initial expansion into many clinical areas, hospitalists' groups are now contracting their scope of practice. More effort is being put into determining which areas are best served by co-management. In those areas where co-management is proven to be effective, there continues to be rapid expansion.

76% of Hospitalists work in some capacity in the Intensive Care Unit (ICU). 58% serve as attending physician [2]. This percentage declines in academic medical centers. There continues to be a shortage of intensivists and debate how to best staff the ICU. In response to this in 2012, the SHM and the Society of Critical Care Medicine (SCCM) published a joint position in which they proposed a one-year critical care fellowship for hospitalists with at least 3 years of experience [13]. Despite these recommendations, no consensus has been reached to address the intensivist shortage.

Turnover Rate for Hospitalists is Trending Downward

Turnover continues to be an issue in many programs. However many groups are finding solutions. The mean yearly turnover rate in 2016 was 6.9%. This rate continues to decline yearly, with a rate of 14% reported in 2010. Nonteaching hospitals

report a significantly lower turnover rate [2]. Although hospital medicine has traditionally been thought to have a high turnover rate, current trends place it near the national average of 6.8%.Turnover among all specialties has increased [14].

Of those leaving a hospitalists position, 45% left for another hospitalist job, 16% left for a fellowship, and 13% left for ambulatory practice. Although reported data is limited, morale seems to be a primary factor in physician retention reported by many program leaders and is a target for retention policies.

Hospitalists are increasingly being recruited from other programs with 36% of new hires coming from another Hospitalist program. 35% were hired directly out of residency. In 2012, 48% of all new hires came directly out of residency.

The cost of recruiting a new physician is variable among practices. According to Cejka Search Associates, a hospitalist group will interview on average three candidates per vacancy filled. The total direct cost on average comes to $31,090 per position filled. These costs do not include credentialing, onboarding, decreased productivity, and other factors which may exceed $100,000 per position filled [15]. Others suggest that overall financial impact on a hospitalist group may be even greater. With these factors in mind hospitalists groups are aggressively implementing methods to improve retention.

Malpractice Trends

The first major study to look at malpractice claims among hospitalists, released in 2013, revealed that the rate of medical malpractice claims is significantly lower for hospitalists compared to nonhospitalist internal medicine physicians [16]. Emergency medicine doctors had nearly a seven times higher rate. The retrospective observational analysis looked at the rates, types, and causes of medical malpractice claims made against hospitalists in the United States. The findings were somewhat unexpected as hospitalists take care of acutely ill patients and malpractice rates were assumed to be as high as Intensivists or Emergency Medicine. Much of this data came from the early years of hospital medicine.

Despite this original study, there is some evidence to suggest that malpractice claims are increasing, as the specialty continues to develop. A 2016 review of closed claims by the Doctor Company, a major provider of malpractice insurance, revealed some interesting trends [17].

Most claims were divided into three primary categories.

1. 36% were diagnosis related. This usually occurred at the initial assessment of the patient. Specific examples with a high frequency included intestinal disorders, such as obstruction or perforation (16%), acute cerebral vascular accident (7%), acute myocardial infarction and cardiac arrest (6%), sepsis and toxic shock syndrome (5%), pulmonary embolism (5%).
2. 31% involved improper management or treatment. This allegation is related to decisions about the patient's care after diagnosis. Examples include inadequate

assessments of wounds and decubitus ulcers resulting in sepsis. Also included were inadequate management of diabetic patients resulting in ketoacidosis. The delayed diagnosis and inadequate treatment of sepsis was also noted as a single prominent causative factor.

3. 11% were attributed to medication-related errors. This included a lack of antibiotics when indicated. Respiratory failure from excessive doses of narcotics was one factor reported. Venous thrombosis in patients with known underlying risk factors for thrombosis that were not anticoagulated was reported. Not stopping anticoagulants prior to surgery was also found. Toxicity resulting from a failure to monitor medications such as gentamycin, vancomycin, and warfarin

One emerging missed diagnosis reported is a spinal epidural abscess, which occurred in 4% of the claims. This is historically an uncommon disease, and rarely reported as a source of malpractice claims. The increase may be due to the increase in the use of intravenous heroin.

Claims arising from hospitalist care are more likely to have a higher injury severity than other physician specialties.

Based on a review of all cases and claims that had been finalized, the physician reviewers of the Doctors Company outlined four fundamental steps to lessen the risk of hospitalist being sued for medical malpractice [17].

1. Early consultation in cases where a potentially serious outcome is anticipated should be considered.
2. Effective communication during handoffs, including specific action plans for potential deteriorating conditions should be employed consistently and system wide.
3. Timely review of all consultation and nursing reports should be performed throughout the day.
4. Noncompliance should be documented with specific language by the patient or family.

Due to an unusual increase in claims made for neurosurgical conditions, specific recommendations were made. When high-risk neurological conditions are identified such as neck, back pain, loss of neurological control or fever, imaging should be ordered STAT to confirm the diagnosis. Surgeons should be consulted early in the diagnostic process to expedite treatment, develop a specific plan, and preserve neurological function.

Career Satisfaction

According to a 2016 Medscape survey, 68% of all hospitalists said they would choose medicine again, but only 36% would select their own specialty. Among 26 medical specialties, this was third from the bottom, with only outpatient Internal Medicine and Nephrology being lower. Only 21% would choose their own practice setting again if given other opportunities [18].

In a prior study in 2011 that focused on lifestyle, 63% of respondents reported high satisfaction with their job and lifestyle it afforded, while 69% were highly satisfied with their specialty. 30%, however, also reported feeling symptom of job burnout [19].

Several studies have compared hospital medicine with other specialties regarding long-term career satisfaction, but no definitive results are available yet. In general, limited studies have concluded that hospitalists enjoy the time off afforded by the specialty but as with many physician practices, there is a trend towards increasing job dissatisfaction.

Although hospital medicine was not specifically surveyed, a 2016 Medscape survey found that the specialties least happy at work were internists (24%) and intensivists (25%). The same report noted that significant burnout that impacted daily functioning was highest at 55% in Critical Care followed by Internal Medicine at 54% [18].

Significantly more physicians in most specialties reported burnout in 2014 than in 2011, according to a recent survey [20]. Physicians in the emergency department reported the highest rate of burnout in the United States.

Hospitalists Morale and the Morale Index

Declining morale has been attributed to several factors by leading hospitalist experts. Reasons cited include rising cost pressure by hospital administrators, decreased autonomy, and the implementation of electronic medical records. The term often expressed is that hospitalists are not performing at the "top of their license" in their daily practice. Clerical work continues to occupy much of the hospitalists day with some studies suggesting that only 10–20% of the day is spent on direct patient care.

Recently a validated hospitalist's morale index was introduced to assess morale and to improve physician retention [21]. The tool measures morale based on five multi-question factors and five single-question items. Research to date indicates that the longevity within the same hospitalist group leads to higher morale, with a dramatic rise at the 36-month mark.

In their initial presentation of the morale index it was noted that a one point increase in morale score was associated with an 85% decrease in the odds of leaving the practice [21].

Future Trends

Salaries should continue to rise in the near future. The market has not yet reached saturation with 20% of Hospitals that have yet to start Hospitalist programs and many programs have unfilled positions or staffing models that are in transition. For every

physician pursuing a job as a hospitalist, there continues to be several job openings available. For this reason, recruitment and retention will continue to be a challenge.

The shift from a volume to a value-based payment system means that hospitals will have an increasing financial relationship with quality measures, readmission rates, core measures, and meaningful use. Hospitalists will be expected to understand and drive that process and ultimately have a greater portion of their salary from that. Collected fees will remain flat. Improved charge collection methods will be maximized in the near future. Salary growth will be more dependent on cost savings as opposed to increased revenues. The task of demonstrating value will become more difficult as fee for service shifts to population management. Prior metrics such as length of stay, wRVUs will decrease in significance as compared to complication rates and readmission rates.

Health care reform will limit hospital admissions, driving more services to the outpatient setting. However, with an aging population, which conversely drives up admissions, the time frame for markedly decreased patient volumes is uncertain. In the next several years there should be a stable if not slight increase in hospital admissions.

More services will be provided at home. In many areas care will continue to shift to the outpatient setting. The near future may see the hospital at home model, become more of reality with hospitalist possibly providing acute services at home. Telemedicine will be a key component of this. The hospitalist will continue to be seen as the acute care specialist wherever that acre is delivered.

Consolidation within healthcare systems will standardize hospitalists programs. There will be substantially fewer hospitals in the future, but those that exist will have greater volumes. Hospital medicine sections will continue to increase in size enjoying both economies and diseconomies of scale. Large programs may need to divide into smaller more manageable sections.

The electronic health record (EHR) has had and will continue to have an enormous impact on the specialty. Hospital medicine is primarily an intellectual profession and is both challenged and supported by the EHR. Certain skills will become obsolete, as new ones will need to be developed.

Malpractice claims may be increasing. Definitive data is not yet available, but trends suggest that increasing scope of practice, block scheduling and expansion of the specialty may be contributing to increased liability exposure for hospitalists.

Advanced practice providers (APP) will continue to expand. APP will become integrated into most programs. So far the data demonstrates that they are cheaper, effective, and have added value to hospital medicine groups. Initial studies have shown their quality to be excellent with no apparent increase in liability. At approximately half the cost of full-time hospitals they are viewed favorably by administration. Their impact on malpractice claims is uncertain at this time, but programs should develop appropriate training and supervision policies as these areas have come under scrutiny in the first wave of malpractice claims review.

Scheduling may become more varied as the 7-day-on 7-day-off model is challenged. The challenge will be to promote continuity both in patient care and in the

administrative duties of the hospital. Some programs receive no subsides from the hospital often by working beyond the model of 7 days on 7 days off.

For a certain subset of chronically ill patients who utilize the greatest resources, the traditional hospitalist model may not be the best option. These patients may be better served by a single physician that manages their care both in the hospital and out.

Conclusion

Hospital medicine is entering its second phase of growth. Those who founded the specialty and were part of the exponential growth are now often transitioning to administration. A specialty that once had unlimited growth is now becoming more introspective on its future growth and development. A new set of leaders with a new set of skills will be needed to define the specialties growth. Growth may not be needed as much as taking the correct path. It can be expected that this phase will be awkward as certain aspects of the practice need to be redefined. As with many specialties, the practice will continue to seek ways to practice meaningful medicine. The struggle to practice at the "top of one's licensee" will continue as diagnostic and therapeutic skills continue to be replaced by standardized guidelines.

Certainly the skill sets of the hospitalist will need to change. The hospitalist will be expected to coordinate a health care team. People management skills will become more prominent. Fortunately for a specialty that is only 20 years old and hasn't yet established what its specific roles are, adaptation to the future should come with reasonable ease. The things that have defined a good hospitalist program—standardization of care, adaptability, good communication with other providers, developing relationships with patients and families—all of those things in the health care system of the future are going to be of tremendous amount of value. The challenge will be in quantifying those attributes, define what success is and develop the skill sets to achieve them.

Key Points

- Currently there are 50,000 Hospitalists in the US. Further growth is expected
- Median salary is $278,471. Mean salary is $297,104
- Base Salary accounts for 80% on average, incentive bonus at 20% is increasing
- Seven days on seven days off is currently the most common schedule
- Physician turnover in Hospitalists groups is declining
- Malpractice claims, traditionally low, may be on the rise
- Career satisfaction, low morale, burnout and retention are ongoing issues

References

1. Wachter RM, Goldman L. The emerging role of the hospitalist in the American health care system. N Engl J Med. 1996;335:514–7.
2. Society of Hopsital Medicine. State of Hopsital Medicine Report. Philadelphia PA: Society of Hopsital Medicine. 2016. p. 1–262.
3. Medical Group Management Association. MGMA Provider Compensation and Provider Publisher Report. Washington DC: Medical Group Management Association. 2016. p. 12–36.
4. Today's Hospitalist (2016) Compensation and Career Satisfaction Survey of 2016. Retrieved from https://www.todayshospitalist.com. March 3, 2017.
5. Medsacpe Hospitalsits Compenastion Report. http://www.medscape.com/features/slideshow/compensation/2016/hospitalist.
6. Yu DJ. The new new metrics. Todays Hopsitalist. 2015;11(9):28–32.
7. Stanik-Hutt J, Newhouse RP, White KM, Johantgen M, Bass EB, Zangaro G, Renee W, Fountain L, Steinwachs DM, Heindel L, Weiner JP. The quality and effectiveness of care provided by nurse practitioners. J Nurse Pract. 2013;9(8):492–500.
8. Hooker R, et al. Does the employment of physician assistants and nurse practitioners increase liability? J Med Licen Discip. 2009;95(2):6–16.
9. Brock DM, Nicholson JG, Hooker RS. Physician assistant and nurse practitioner malpractice trends. Medical Care Research and Review. 2016:1–12.
10. Society of Hospital Medicine. Annual meeting. San Diego Bob Wachter presentation. 2016.
11. Elliott DJ, Young RS, Brice J, Aguiar R, Kolm P. Effect of hospitalist workload on the quality and efficiency of care. JAMA Intern Med. 2014;174(5):786–93. doi:10.1001/jamainternmed.2014.300.
12. Reese SM. Women MDs spend more time with patients: Does it matter? Medscape Bus Med. June 23, 2011. http://www.medscape.com/viewarticle/744653 Accessed 21 Nov 2016.
13. Siegal EM, Dressler DD, Dichter JR, Gorman MJ, Lipsett PA. Training a hospitalist workforce to address the intensivist shortage in american hospitals: a position paper from the society of hospital medicine and the society of critical care medicine. J Hosp Med. 2012;7:359–64. doi:10.1002/jhm.1942.
14. AMGA and Cekka survey 2014. http://www.amga.org/wcm/AboutAMGA/News/2014/082114.aspx. Accessed 15 Jan 2017.
15. NEJMCareerCenter. Recruting Physicians Today. May/June 2012:20(13) www.employer.nejmcareer.org. Accessed 10 Feb 2017.
16. Hospital Medicine. Society of Hospital Medicine (SHM) annual meeting. 2013. Presented on May 18, 2013.
17. The Doctors Company. Hopsitalists closed claims study. Napa CA: The Doctors Company;2016. www.thedoctorscom/ecm/groups/public@tdc/@web@kc@patientsafety/documen. Accessed 01 Feb 2017.
18. Medscape career satisfaction survey 2016.
19. Hinami K, Whelan CT, Wolosin RJ, Miller JA, Wetterneck TB. Worklife and satisfaction of hospitalists: toward flourishing careers [published online ahead of print July 20, 2011]. J Gen Intern Med. doi:10.1007/s116060-011-1780-z.
20. Shanafelt TD, Hasan O, Dyrbye LN, Sinsky C, Satele D, Sloan J, West CP. Changes in burnout and satisfaction with work-life balance in physicians and the general US working population between 2011 and 2014. Mayo Clin Proc. 2015;90:1600–13.
21. Chandra S, Wright SM, Ghazarian S, Kargul GM, Howell EE. Introducing the Hospitalist Morale Index: a new tool that may be relevant for improving provider retention. J Hosp Med. 2016;11:425–31.

Chapter 19
The Background and Development of Hospital Medicine as a Specialty Globally: The Challenges of International Hospital Medicine

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Introduction

Hospital medicine has emerged as a specialty at various rates among different countries. The forces that drove this rapid expansion in the United States exist in varying degrees in other countries. From the perspective of physicians practicing outside of the United States the growth of hospital medicine has been both educational and an important guide for what may occur in our own practices.

From the international perspective, hospital medicine in the United States emerged through a deficiency within the accepted care model. Robert Wachter introduced the term "hospitalist" in the famous NEJM article [1]. In 1996 there were probably a few 100 practicing Hospital-Based Physicians in the US. Even for conditions that required specialty care such as cardiac surgery or childbirth, the expectation was that the patient's "regular doctor" would manage the daily medical care.

For hospitalizations not requiring specialty care, such as diabetes, myocardial infarction, stroke, or severe infections—the patient's primary care doctor served as the attending, consultants were called in for advice or procedures as needed. In contrast in other countries, the patient's "regular doctor" was not expected to come to the hospital; rather, a hospital-based physician (with some differences from the US hospitalist system, that will be addressed ahead) would assume the responsibility for hospital care. Even before results in efficiency, quality improvement, patient safety, and patient experience were reported, the US Hospitalists movement gained a great deal of international visibility.

While international hospital medicine has gradually expanded, US hospital medicine has advanced at an exponential growth rate. Its rapid growth has been observed as an example of the adaptability and the ability of economics to drive rapid change in the United Sates (US) health system.

Outside of the US, there have been limited publications generated from the field of hospital medicine. US hospitalists continue to produce the most significant scientific publications. In addition, US hospitalists lead the way in demonstrating value and the development of significant benchmarks.

Importantly, other countries have already been functioning with a hospital-based physician. Internationally, subspecialists have usually assumed the role of ward-based physicians. Generalists are now assuming this position. This has occurred in part due to developments in US based practices.

Hospital Medicine Outside the United States

Hospital Medicine in Canada

Hospital medicine in Canada emerged during the 1990s when the first programs appeared in response to a growing number of "unattached" patients [2, 3, 4]. Unattached (also called "orphan" patients) are those who either did not have a family physician, or if they did, their family doctors did not deliver inpatient care.

Historically, family physicians are essential to the healthcare system of Canada. Traditionally, physicians followed their own patients when they required admission to the hospital. While this continues to be the case in small rural and semi-rural communities, a number of fundamental shifts in the healthcare system throughout the 1980s and 1990s resulted in a shortage of family physicians. These included a reduction in medical school enrolment in the 1990s (as a result of an economic recession and government cut-backs in medical education) and a growing population (especially an older population with a higher burden of chronic diseases). As a result, the College of Family Physicians of Canada estimated that in 2008, 4.6 million Canadians did not have a family physician [5].

At the same time, many family physicians gradually reduced the scope of services they provided, choosing to focus their practiced primarily on an outpatient setting. For example, the percentage of Ontario family physicians providing only office-based care increased from 14% in 1989–1990 to 24% in 1999–2000 [6]. This was due to several reasons: limited physician supply and the higher workload, sicker patients with more chronic illnesses in the community (further increasing workload in the office), increased importance of work–life balance and inadequate compensation for hospital care [5, 8–10]. As a result, having access to a family physician in the community did not necessarily mean that patients would have a provider when they needed to be admitted to a hospital for acute illnesses. The hospitalist model was initially developed as a response to this challenge.

Since the first hospitalist programs began in the late 1990s, the Canadian hospitalist model has seen an exponential growth. Studies done by the Canadian Society of Hospital Medicine reveal that while the number of identified full-time equivalent hospitalists has increased 3.4 fold between 2002 and 2006, the number of programs has increased from 1 in 1998 to 100 in 2008 [4]. In 2012, there were at least 102 hospital corporations with active hospital medicine programs in Canada, with some of these institutions having multiple hospitalist programs in each of their facilities. Most programs were a decade into their development. About 50% of self-identified hospitalists in the survey have been working in this field for 10 years or more, with the majority of respondents working in large community hospitals. Over 86% percent of survey participants were credentialed by the College of Family Physicians of Canada, and 11.5% percent had undergone advanced training in hospital medicine. Most respondents indicated that their hospital medicine program's scope of practice went beyond what had traditionally been provided by community-based general practitioners, and up to 80% of respondents were involved in non-clinical activities such as quality improvement initiatives, hospital committee participation, and teaching.

There is growing evidence that hospital medicine programs improve the efficiency of care in Canada. Table 19.1 summarizes the literature on the impact of hospitalist programs on length of stay and mortality [10, 11].

Canadian hospitalists have followed their American counterparts by taking on a leading role in the patient safety and quality movement. In many organizations, hospitalists are involved in systemic quality improvement projects and are at times early adopters of such efforts. Canadian hospitalists are the natural allies for health system leaders and managers in their quest to find innovative solutions for better value delivery and patient-centered care.

Table 19.1 Summarizes the literature on the impact of hospitalist programs on length of stay and mortality

Study, year	Type of facility	Province	Length of stay (days)	Bed days	Readmission	Staff satisfaction	Mortality
Advisory Board (2015) [8]	Medium community hospital	ON	8	8	8	6	N/A
Seth et al. (2015) [9]	Medium community hospital	ON	8	N/A	6	N/A	N/A
McGowen (2003) [10]	Medium community hospital	BC	8	8	8	N/A	N/A
Norris (2011) [11]	Academic tertiary hospital	ON	5, 9	N/A	N/A	N/A	N/A
Yousefi (2011) [12]	Large community hospital	ON	8	N/A	8	N/A	8
Webster et al. (2012) [13]	Specialized orthopedic hospital	ON	N/A	N/A	N/A	6	N/A
Conn et al. (2012) [14]	5 large community hospitals	ON	N/A	N/A	N/A	6	N/A

Hospital Medicine in Brazil

The expansion of Hospital Medicine in Brazil coincided with overall reforms in the healthcare system. Until the year 2000, there were no Brazilian publications related to hospital medicine or hospitalists. The first organized efforts to promote the hospitalist model were led by a co-author of this chapter, Guilherme Brauner Barcellos. From 2004 to the end of the decade, slow progress was made in establishing a hospitalist movement. This occurred primarily through informal means, such as websites, blogs, and local meetings. In 2010 a milestone Pan-American event in the city of Florianopolis was organized. This included speakers from the United States, as well as Chile, Argentina, and Brazil. International collaborations developed with the United States established the Society of Hospital Medicine (SHM). Several key physicians from the United States supported these efforts, including Neil Winawer (Emory University), Aleta Borrud (Mayo Clinic), and Ron Greeno (SHM). These hospitalists attended five of the early meetings in Brazil from 2008 to 2016. Ron Greeno was the keynote speaker at one of the most recent meetings.

In 1996, Brazil established a health system based on decentralized universal access. Individual municipalities were given the task of providing comprehensive and free healthcare to its population. The states and federal government financed this. There continued to be both a public and private system during this period of

expansion. It became increasingly difficult to provide care with the old model of physicians serving as both in-patient and out-patient providers. There were few established hospitalists at this time. The United States hospitalists movement was seen as an opportunity to meet the challenges of universal care and at the same time deliver patient-centered care.

The Brazilian public system had traditionally operated with a hospitalist model. This system was often under stress due to lack of resources, poor management, and excessive workloads placed on practitioners. Despite laws defining work hours, many hospitals exceeded these regulations and quality suffered. With few accepted guidelines, administrators pushed the system to its limits.

When attempts were made to establish a hospital system based on the guidelines presented by the Society of Hospital Medicine, several factors were lacking. First a curriculum for the medical students and residents was not well established and incorporated into the programs. Second, the excessive workload prevented physicians from having time for non-clinical activities. There were no financial incentives for efficiency or quality improvement for patient safety. Many programs struggled to meet the expectations of both physicians and administrators.

In the private system, there has been discussion and debate over the role of hospitalist physician. This is due to pressure from patients and families that see themselves as clients in the private system. There has also been some reforms influenced by regulatory organizations, such as governmental accrediting agencies. These forces have caused new models to be developed. For example, the model of reimbursement that has evolved from the fee-for-service model to one that promotes quality and patient safety. This has reflected to a small degree the changes seen in the US.

Brazil hospitals are hiring newly trained physicians to work in parallel with the traditional model. The patient's primary physician remains as an overall coordinator for care, who remains outside of the hospital while the hospital-based physician lends assistance. This is primarily for emergency needs, such as filling gaps of the regular care or for nurses' convenience. This system meets the needs defined in Section three of the Core Competencies in Hospital Medicine [12] . While this system has benefits, there are some issues. The conflict is between the physician providing individual care and the supervising physician dealing with system issues. This often results in fragmentation and inefficient care.

Too many Brazilian doctors are splitting their time between public and private systems, which undermines overall efficiency. Job security and financial considerations forces many physicians to work at multiple hospitals due to uncertain administrators actions.

Despite challenges, hospital medicine programs that are similar to ones in the United States and Canada are emerging and publishing their positive findings. Brazil is not yet seeing reductions in length of stays that were seen in the early stages of the US program [13]. Programs where there is a strong sense of ownership (this could be a mindset, not necessarily a legal description—a situation where hospitalists think of the practice as belonging to themselves, not someone else) find the best results. This covers all the dimensions of the Institute for Healthcare Improvement

Triple Aim, which are improving the patient experience of care, improving the health of populations, and reducing the per capita cost of health care. The final aim is to approve professional satisfaction.

In Brazil, only recently has hospital medicine become a recognized specialty. One of the more established groups, the Academia Brasileira de Medicina Hospital, is trying to congregate and promote hospital medicine. The SHM has been extremely valuable in providing guidelines for future development.

Hospital Medicine in the United Kingdom

Most health care in the United Kingdom is provided by the National Health Service (NHS), which was founded in 1948. It is both praised for its cost-effective success, scope of services and criticized for its top-heavy bureaucracy by physicians and citizens alike of the country. To a great extent, the NHS determines the evolution of healthcare in the UK.

Britain often uses the US healthcare system as a benchmark in its own development. The US system is admired for its autonomy but cautiously observed for its outcomes. Like many developed countries, Britain ranks above the US in many health measurements [14]. It is uncertain if this is due to its healthcare system or lifestyle of its population. Its citizens have a longer life expectancy, suffer few in-hospital complications, and have a lower infant mortality. Despite a limited budget, there are more acute care hospital beds per capita and fewer deaths related to surgical or medical mishaps. Britain achieves these results while spending annually about $2500 per person in Britain, compared with $6000 in the US [20]. In addition to its widely used public system, there is a private insurance structure.

Under the influences of a centralized health care system, hospital medicine has evolved in a parallel manner in the United Kingdom. Fifteen years ago acute care medical units (AMU) were established to meet the needs of increasingly complicated in patients [15]. Until that time most inpatients were primarily managed on specialty wards, and this occurred primarily during daytime and weekday hours. It was recognized that hospital patients were increasingly complicated and would benefit from timely management by physicians with a more general background and with dedicated training in acute medicine.

The Royal College of Physicians published a report in 1998 emphasizing the need for improvement in patient management [15]. Further discussions led to the development of acute medicine as a dedicated specialty, and in 2003 it was recognized as a subspecialty of General Internal Medicine [1]. In 2009 it was recognized as a separate specialty with formal training programs developed.

Several differences in practice style exist between US and acute care physicians. They largely limit their work to the AMU. Patients are located in a single geographic unit allowing for greater efficiency. The AMU is a combination of a US step-down unit, an ED observation ward, and an extended stay in an emergency department. The volumes are high, with frequent transitions and discharges.

Co-management of patients has not been developed as in the United Sates and the scope of practice remains limited.

Approximately 50% of patients admitted to the AMU require hospital stays longer than 48 to 72 h [16]. They must be handed off to one of the subspecialty wards. There is still the consensus among patients and the healthcare system that patients with focused problems, which do not resolve in the first 48 h may be best served on subspecialty services.

The number of acute physicians has grown rapidly but not at the exponential rate that US hospital medicine has. There is concern that rapid growth would lead to the devaluation of the new specialty. There has been an emphasis on developing the correct training protocols before there is rapid expansion [17]. Most hospitals in Great Britain have an AMU and employed acute care physicians, although their groups tend to be much smaller.

Traditionally, most units cover weekdays only with junior physicians covering nights and weekends. There has been the trend to cover the units seven days per week, with increasing coverage at night. This is usually accomplished with rotating staff covering weekends as opposed to a seven-day block schedule.

As with the US studies, several studies have demonstrated their effectiveness in reducing mortality and reducing overall costs.

Some policies dictated by the National Health Service in Great Britain markedly influence specialty choice. A senior General Practitioner can make the equivalent of $300 K/year in US dollars, substantially more than the average specialist. Many medical trainees in Britain choose primary care careers for the financial incentives [17]. For these factors recruitment of acute care physicians has at times been a challenge. Reforms have been suggested to increase training slots and practice opportunities in acute care medicine to meet the continued growth of the specialty.

Hospital Medicine in Argentina

Despite having pockets of hospitalists programs growing around the country, the hospitalist's movement in Argentina has not gained the momentum that it has achieved in other countries. In order to provide an actual view of the current state of affairs, we conducted a search in PUBMED using the MESH terms "Argentina" and "Hospitalists" and we could not find any peer-reviewed studies or reviews commenting on the performance of hospitalists programs have in Argentina. The search was supplemented with a gray literature search, with provided some non-peer-reviewed information.

There have been attempts to create a society or group that will take the lead at developing hospital medicine as a specialty, but they have not flourished. Also, there have been some international conferences and courses created to introduce the hospitalist movement to Argentina, the last being in 2016 (fifth edition of the Argentinian Congress of Hospital Medicine that takes place simultaneously with National Internal Medicine Congress).

The explanation of why this movement has not caught on in Argentina could lie in the way training and practice regulations occur in Argentina. Argentina has a multi-payer system including private hospitals, union run hospitals, national hospitals and provincial hospitals making policies on how to provide care difficult to implement. Furthermore, there is no unifying board of medicine (such as the American Board of Internal Medicine or Royal College of Physicians and Surgeons) which could support the development of an agenda towards hospital medicine. Another explanation could be that physicians are commonly required to work at multiple places or have to run their own private practices to supplement their income not allowing to have full-time dedication at a single institution to take care specifically of inpatients. Also, many physicians support themselves working as nocturnists or "on-call" doctors generally covering general medicine wards and/or emergency simultaneously.

In the future, and to warranty the development of hospitalists programs, payers and institutions should facilitate full-time dedication to inpatient care as a recognized specialty. The outcome and quality of these programs should be careful monitored and reported to ensure that they provide the same valuable care as they do in other countries.

Hospital Medicine in Spain

The first recognized program of Hospital Medicine in Spain was founded a decade ago, at the "Clínica Universidad de Navarra," in Pamplona. The program was run for internal medicine specialists whom dedicated more than 90% of their time to the care of hospitalized patients. Since then, many other private and public health centers developed local programs inside the internal medicine departments, around the country, and were mainly focused on perioperative co-management with orthopedics and general surgery. Nonetheless, the Spanish medical societies do not recognize the term "Hospital Medicine" and neither the special work of the hospitalists among the clinical specialties. In fact, many internists work in urban and rural centers as hospitalists, but they didn't know the implications and the potential special issues regarding training that "Hospital Medicine" implies.

Currently, Spain is working to develop local chapters of hospital medicine inside the Spanish Society of Internal Medicine. However, they need time and significant modifications in the health care system infrastructure to be organized in a similar way such as the US SHM society. In this context, differences in health care organization around the world could explain the limitations to expand Hospital Medicine programs in Europe. Specifically, in Spain, the National Health Care System (NHCS) provides an integral health coverage for Spanish and European citizens, based on public and regional administration payments. Actually, the national insurance contribution corresponds to 6–7.5% of the salary, and in global terms Spain invests the 9.5% of the GDP in Health. The "hospitalists" are mainly salaried employees, in public and also private academic medical centers. Therefore, to obtain

recognition as "hospitalists" and in the same way to expand the local programs nationwide, we need political and economical modifications in the parent health care system to establish the concept of Hospital Medicine.

Nevertheless, Spanish hospitalists are working to develop new clinical practice models, to improve the care of complex patients, expand co-management, and increase the teaching potential of Hospital Medicine, using specialized units such as intermediate care areas [17, 18]. In this setting, they are also working in mortality prediction models for intermediate care patients developing specific scores for this population [19, 20] and also for patients undergoing non-invasive mechanical ventilation [21].

The government and the medical board are trying to improve the organization of the medical specialties, with substantial modifications in the current programs for medical training. Rather than apply directly to subspecialties, the system will be similar than the US programs, based on 2–3 years of training in internal medicine. At the core of these modifications is the need to improve the resource distribution and the application in more rational way. This is going to be a significant opportunity to develop the idea of hospital medicine in Spain, through specific modifications in the current curriculum of Internal Medicine programs.

The hospitalists in Spain have to develop and apply the best practice models in their respective centers. In the same way they have to work on quality improvement, clinical research, co-management, perioperative medicine and increase the potential opportunities for teaching. In this scenario, the mentoring from recognized centers in US could be of great help. The future development of Hospital Medicine in Spain also depends on the identification of the main problems and limitations of the current programs. In this setting it's necessary to obtain in the near future, nationwide data, regarding length of hospital stay, nosocomial complications, mortality, readmissions and costs adjusted by AP-DRG.

Hospital Medicine in Taiwan

In Taiwan, the Chang Gung Memorial Hospital (CGMH) introduced the first trial of hospitalist system in 2002, handled by a group of young attending physicians in the internal medicine department. However, the group structure, shift schedule, and clinical performance did not publish in the literature, but it is currently running with a 50-bed scale. In 2009, the National Taiwan University Hospital (NTUH), the top public medical center in Taiwan, established a new acute care ward that introduced the system of hospital medicine from the United States. This new hospitalist ward provided care to acute general medical patients awaiting admission in the emergency department. The performance of this pioneer hospitalist ward in NTUH, being efficient and cost saving without compromise of patient outcome, was published in 2011 [23]. Three pioneer hospitalists were sent to the US as visiting scholars, who visited at least eight hospitals across the western, central and eastern America and brought back valuable information for Taiwan. After that, the newly

developed hospitalist system at NTUH became the benchmark of hospital medicine in Taiwan. In 2011, NTUH won the National Human Resource Design Innovation Prize by this new hospitalist team.

Since 2010, Taiwan was facing a shortage of primary care workforce, both in the community and the hospitals. Internal medicine is one of these specialties which lacked house staff, and the shortage of manpower in the hospital resulted in increased burden of attending physicians who traditionally provided both outpatient and inpatient care. Furthermore, malpractice liability has abnormally increased in recent decades in Taiwan, which led to the unwillingness of physicians to care for acutely ill hospitalized patients.

In order to solve these problems, the Ministry of Health and Welfare (MHW) of Taiwan has proposed several solutions. First, efforts are made to improve the labor of the internal medicine and surgery residency training by the work hour restriction of 88 h per weeks. Second, burden of malpractice liability must be mitigated with laws and relief systems for adverse clinical outcomes. Third, hospitalist system could be considered as a new workforce to cope with shortage of first-line manpower in the hospitals. However, the pioneer hospitalists in NTUH offered their values more than just to be surrogate manpower. This team proved that hospitalists can participate in intelligence technology, quality improvement, hospice palliative care [24, 25], post-discharge transitional care [26], and physician workload evaluation [27].

The MHW of Taiwan is currently promoting a nationwide project of hospital medicine since July 2015. Although unpublished, most of the 19 hospitals within this project in 2015 generated positive results of either quality improvement or cost saving, or both. Until 2016, the number of hospitalists was around 150 in this country. The policy makers and the public health sectors are continuing seeking the values of hospital medicine implementation for hospitals in different levels, sizes and regions. In 2016, the MHW of Taiwan decided to give hospitalist a specialty that was certified by the government. Hospital medicine in Taiwan is expected to greatly prosper in the near future.

Other Experiences Around the World

Chile

In Latin America, it's important to view the experience of the Chileans. In Chile there are hospitalist programs in Hospital Clinico de la Pontificia Universidad Catolica de Chile and Clinica Alemanha de Santiago. The first group attended the international hospital medicine meetings in the city of Santiago and was chosen as the best hospitalist case presentations in a Pan-American meeting of hospitalists. They were competing with others from Brazil and Argentina. The second group was able to reduce the average length of stay in 50% and to "created" extra beds in the hospital. Bernd Oberpaur, Deputy CMO in Charge of Projects, Clinica Alemanha de Santiago, said to Advisory Board that "the initial investment was to establish a

contractual relationship with the hospitalists, in order to ensure continuous, optimal, and 24/7 care under specific action protocols. The justification: it is much cheaper to invest in hospitalists than to add more beds.

Singapore

From Asia there is a publication with the results of family physician developed hospitalist program in the Singapore General Hospital (SGH) as generalists dedicated for the hospital [28]. The study showed improvements in length of stay and cost reductions with hospitalists. There were no difference in mortality and readmissions. According to the authors of the article, tertiary hospitals in the Singapore health system grapple with the challenges of providing highly subspecialized care to patients who at the same time requires general medical care for multiple complex comorbidities. Concerned with the care by subspecialists and fragmentation, SGH developed a hospitalist model of care based in a generalist as hospitalist. It is well known that several countries in Europe are changing or at least debating the modification from a subspecialist to a generalist as the ward-based physician most responsible for the patients during hospitalizations.

The Middle East

In the Middle East, doctors from the United Arab Emirates, Qatar, and Saudi Arabia have launched the Middle East Chapter of the SHM. At Cleveland Clinic Abu Dhabi they have a dedicated hospitalist program, but in the majority of the hospitals there they still have a traditional model. Anand Kartha, a hospitalist from Qatar, said recently for the Journal of Hospital Medicine that their program is flourishing. There are several factors driving hospitalist model of care in Qatar that include pressures to improve efficiency, throughput, and quality of care.

Challenges in Common and Conclusions

As is evident, geographically dispersed countries have similar reasons to invest in hospitalists. Patients with multiple morbidities are the most common presentation to hospitals around the world. Adults commonly have multiple chronic conditions and are the major users of health care services. They account for significant health care spending, and regardless of the health care system in place, hospital medicine provides for an efficient manner to provide for their care. All countries, regardless of their financial situation, are coming under increased pressure improve efficiency, throughput, quality of care, and patient safety.

There are demographic and financial differences between countries, but we could not find any that would not benefit from a hospitalist model a care. Collaboration among physicians worldwide is needed to promote this specialty. Each country has a unique and valid manner in which healthcare is delivered in the hospital, most bound to some degree by tradition.

References

1. Wachter RM, Goldman L. The emerging role of "hospitalists" in the American health care system. N Engl J Med. 1996;335(7):514–7.
2. Yousefi V, Wilton D. Redesigning hospital care: learning from the experience of hospital medicine in Canada. J Global Health Care Syst. 2011;1:1–10.
3. Canadian Society of Hospital Medicine [Internet]. Vancouver: Canadian Society of Hospital Medicine c 2009–2010. The 2008 Canadian Hospitalist Compensation and Workload Survey. [cited 2010/10/26]. Available from: https://canadianhospitalist.ca/content/cshm-survey-results.
4. Supporting the Future of Family Medicine in Canada, Is enough being done today to prepare for tomorrow? Report Card. Mississauga ON: College of Family Physicians of Canada, 2008.
5. Chan BT. The declining comprehensiveness of primary care. CMAJ. 2002;166(4):429–34.
6. Day A, MacMillan L. Neglect of the inpatient: the hospitalist movement in Canada responds. Hosp Q. 2001;4(4):36–41.
7. Stewart A. Hospitalism in Ontario: from crisis management to opportunity. Ont Med Rev. 2003;70:33–9.
8. Seth P, Nicholson K, Habbous S, Ménard J. Implementation of a hospitalist medicine model in a full-service community hospital: examining impact two years post-implementation on health resource use and patient satisfaction. Abstract Submitted to Canadian Society of Hospital Medicine Annual Conference. 2015.
9. McGowen B, Nightingale M. The hospitalist program: a new specialty on the horizon in acute care medicine, a hospital case study. BCMJ. 2003;45(8):391–4.
10. Yousefi V, Chong CA. Does implementation of a hospitalist program in a Canadian community hospital improve measures of quality of care and utilization? An observational comparative analysis of hospitalists vs. traditional care providers. BMC Health Serv Res. 2013;13:204–11.
11. Webster F, Bremner S, Jackson M, Bansal V, Sale J. The impact of a hospitalist on role boundaries in an orthopedic environment. J Multidiscip Healthc. 2012;5:249–56.
12. The core competencies in hospital medicine: a framework for curriculum development by the society of hospital medicine. J Hosp Med. 2006; 1:(Suppl 1):2–95.
13. Grohs LB, Daltoe T et al. Medicina Hospitalar como ferramenta de segurança: comparação do desempenho de médicos hospitalistas com equipe de cuidados tradicionais no Sistema Único de Saúde do Brasil. Rev Soc Bras Clin Med. 2013; out-dez.
14. Dowdle JR. Acute medicine: past, present, and future. Emerg Med J. 2004;21(6):652–3. doi:10.1136/emj.2003.012211.
15. Royal College of Physicians. Acute medical admissions and the future of general medicine. Edinburgh and Glasgow: Scottish Intercollegiate Working Party; 1998.
16. Scott I, Vaughan L, Bell D. Effectiveness of acute medical units in hospitals: a systematic review. Int J Qual Health Care. 2009;21(6):397–407. doi:10.1093/intqhc/mzp045.
17. Stein A, Henley J. Acute medicine: do we need 'medical traffic wardens' to make us interested in general medical patients? QJM. 2007;100(7):463–4. doi:10.1093/qjmed/hcm037.
18. Carmona-Torre F, Martinez-Urbistondo D, Landecho MF, Lucena JF. Surviving sepsis in an intermediate care unit. Lancet Infect Dis. 2013;13(4):294–5.
19. Lucena JF, Alegre F, Martinez-Urbistondo D, Landecho MF, et al. Performance of SAPS II and SAPS 3 in intermediate care. PLoS One. 2013;8(10):e77229.

20. Lucena JF, Alegre F, Martinez-Urbistondo D, Landecho MF, Huerta A, García-Mouriz A, García N, Quiroga J. Performance of SAPS II and SAPS 3 in intermediate care. PLoS One. 2013;8(10):e77229.
21. Alegre F, Landecho MF, Huerta A, Fernandez-Ros N, Martinez-Urbistondo D, García N, Quiroga J, Lucena JF. Design and performance of a new severity score for intermediate care. PLoS One. 2015;10(6):e0130989.
22. Martinez-Urbistondo D, Alegre F, Carmona-Torre F, Huerta A, Fernandez-Ros N, Landecho MF, García-Mouriz A, Núñez-Córdoba JM, García N, Quiroga J, Lucena JF. Mortality prediction in patients undergoing non-invasive ventilation in intermediate care. PLoS One. 2015;10(10):e0139702.
23. Shu CC, Lin JW, Lin YF, Hsu NC, Ko WJ. Evaluating the performance of a hospitalist system in Taiwan: a pioneer study for nationwide health insurance in Asia. J Hosp Med. 2011;6(7):378–82.
24. Hsu NC, Lin YF, Shu CC, Yang MC, Ko WJ. Noncancer palliative care: the lost pieces in an acute care setting in Taiwan. Am J Hosp Palliat Care. 2013;30(4):334–8.
25. Hsu NC, Chang RE, Tsai HB, Lin YF, Shu CC, Ko WJ, Yu CJ. After-hours physician care for patients with do-not-resuscitate orders: an observational cohort study. Palliat Med. 2014;28(3):281–7.
26. Shu CC, Hsu NC, Lin YF, Wang JY, Lin JW, Ko WJ. Integrated postdischarge transitional care in a hospitalist system to improve discharge outcome: an experimental study. BMC Med. 2011;9:96.
27. Hsu NC, Huang CC, Jerng JS, Hsu CH, Yang MC, Chang RE, Ko WJ, Yu CJ. Influence of patient and provider factors on the workload of on-call physicians: a general internal medicine cohort observational study. Medicine (Baltimore). 2016;95(35):e4719.
28. Hock Lee K, Yang Y. And cols. Bringing generalists into the hospital: outcomes of a family medicine hospitalist model in Singapore. J Hosp Med. 2011;6(3):115–21.

Chapter 20
Tools for Applying Medical Knowledge

Kjell Benson

Introduction

> Medicine is not itself a science. Despite its reliance on a well-stocked fund of scientific knowledge and its use of technology, it is still a practice: the care of sick people and the prevention of disease [1].

Every day, as we encounter patients face-to-face, clinicians are reminded that the task at hand is not strictly scientific. Clinicians treat individuals, and individual cases. And yet doctors also need to dedicate themselves to mastery of the "well-stocked fund of scientific knowledge." This dialectic between generalized knowledge and individual humans constitutes the clinician's enigma, and is the subject of this chapter.

The patient encounter consists of an inescapable singularity between two people at a moment in time. Even with the same pathological process, no two cases are ever the same. The coalescence of that particular time, that patient, that clinician, and that disease occurs only once, ever. When clinicians lose sight of the individual in front of them, the criticisms of Western medicine blossom: paternalism, sterility, and futility. Yet patients also expect the application of the entire armamentarium of scientific knowledge to their particular case. Our society has invested heavily in studying generic scientific entities such as "heart disease" and patients want the benefit of all this research. So modern Western medicine has staked its reputation on this delicate balance between "art and science." Veering over into pure individualism takes one into spiritualism and faith-healing; over-reliance on pure science leads to scientism and hopelessness. Negotiating the knife-edge of clinical practice takes training, constant reflection, and a familiarity with the required tools. Medical training has emphasized our scientific fund of knowledge but has not always been clear about the origin of scientific tools and how those origins affect their application.

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Why do we cite studies when we decide on care? How do we know illness will proceed in the course we predict? How much of what we tell to patients is scientific versus something else?

Hospital admission creates a unique moment of existential crisis in patient lives as they encounter the collision of serious illness, a complex medical system, and a vast quantity of scientific information. The goal of this chapter will be to uncover assumptions hospitalists use in applying this medical knowledge on individual and group levels in order to better care for patients. Philosophical reflection will be seen not as a dry abstract pursuit, but one that is rich in the details of human existence, and one that we all already employ every day in our medical practices. By the end of the chapter I hope you will have a new appreciation of how clinicians apply medical knowledge which will, in turn, foster your own ongoing reflections on the philosophy of medicine.

The Origins of Medical Knowledge

Western medicine's roots in classical Greek thought have been well described [2]. Prior to Hippocrates, illness was thought of as a magical process or the outcome of divine intervention. The Hippocrates and his followers ascribed natural causes to disease, and thus was born what came to be distinctive about Western medicine: a focus on empirical observations and closely described precise physical symptoms and responses. Recently, philosophers have also pointed out that medicine's distinctiveness may also be due to the Greek notions of *phronesis*, or practical wisdom, and *nous*, or intuitive understanding [3].

Practical wisdom was described by Aristotle as the use of reason in everyday situations with the goal of improving human life:

> Phronesis, then, must be a reasoned and true state of capacity to act with regard to human goods [4].

Aristotle required rational thought, combined with action, with a goal of human service. Commentators have remarked how well this formulation seems to fit the physician–patient relationship:

> (1) Phronesis deals with human affairs…; (2) it deals with things that can be otherwise; (3) it deals with things that have a telos [a known goal]; (4) for phronesis it is more important to know… the particular situation, and to reach a decision here and now, than to know only the principles in a universal and abstract way [3].

Abstract principles may be fine for philosophers, but clinicians are required to act in particular situations, and always for the good of their patients. Reflecting on a day of practice in the hospital, most clinicians realize they used more "practical wisdom" than true science. There is a practicality in counseling patients on the treatment of warts or the sniffles that will likely never be transcended by more complex science.

However, practical medicine is not sufficient to define medical practice, as practicality is a ubiquitous trait of human experience, and not unique to physicians. Medicine becomes unique by combining scientific facts, "[which] are known through a process of induction, [and] intuition which is knowledge of first principles" [3]. A thorough *intuitive* understanding of a set of first principles defines medicine.

The "first principles" that early Greek physicians relied upon are scarcely recognizable to us today—humors and temperaments—yet the fact that they combined empirical observations with a set of first principles was an innovation that has laid the groundwork for all subsequent advances. Today, medical students enter school with (hopefully) a solid foundation of practical wisdom, and then are exposed to two full years of "first principles"—the basic sciences. They then add to these first principles with an exposure to actual pathology, and the natural history of diseases. The intuitive grasp of health and sickness engendered by these first principles forms the foundation of all future patient encounters (see Table 20.1).

This intuitive knowledge was the first tool of the physician, and despite its limitations, still remains so. Contradicting our intuitive assessments often forms the impetus for ongoing medical advances. Patients and beginning students often believe that we need to treat the blood sugar level in diabetic ketoacidosis (DKA). But, after seeing the disastrous results of ignoring the acidosis, the intuitive sense that the problem is high blood sugar is corrected. And yet, despite all the myriad examples of intuitive errors, an expert clinician is often judged by peers as being an expert just because of their well-developed *intuitive* skills. The student and resident soon absorbs a new intuitive understanding of DKA treatment, and may by the end of the internship nearly forget why they are treating to the anion gap rather than the blood sugar level. What I know intuitively now is not what I knew intuitively as a child. Intuition is a remarkably adaptable tool.

Despite advances in cognitive science and pedagogy, the Aristotelian description of practical wisdom and intuition continue to describe the most basic processes of today's clinical thought. When we encounter situations that have no precise analogue in sophisticated scientific studies, when we try to apply our clinical knowledge to patients, we inevitably come back to skills in *phronesis* and *nous*. Medical training and residency teach an enormous quantity of "facts" that successful doctors memorize, but they also refine our practical wisdom and intuition.

The next tool in the clinician's toolkit, and the next historical step in developing evidence, represents a logical progression from individual intuition: collective intuition, or the expert consensus conference. Miriam Solomon gives a review of

Table 20.1 Foundations of Patient Encounters

Modalities of medical knowledge
Wisdom and intuition
Expert consensus
Evidence based medicine
Narrative

the development of consensus as a medical tool in *Making Medical Knowledge*, "The NIH Consensus Development Conference Program began in 1977 and ended in 2013" [5]. This single statement encapsulates the entire movement, which is already considered outmoded due to more "scientific" approaches, but which remarkably sticks around, as anyone who has participated in medical staff committee work, or specialty society consensus statements, can attest. We still meet as "expert clinicians," in various decision-making bodies, and through our collective "intuition" guide best practice care. Indeed, one of the draws of practicing hospital medicine is the team approach usually undertaken, in comparison to the inevitable individualism of the clinic provider. Hospitalists often discuss cases with colleagues just to obtain the group consensus.

The Evidence-Based Medicine (EBM) movement supplanted experts in their role as arbiters of medical knowledge. Translational medicine, which moves basic science knowledge from the lab to clinical application, and evidence-based medicine, which verifies the actual utility of treatments in patient care, are the two main elements of modern scientific medicine. Anthologies such as this *Update in Hospital Medicine* appropriately rely on EBM to inform their treatment recommendations. The clinician's main role can now be seen as the translator of EBM for their patients. The clinician functions as an interpreter of statistics for the patient and the public.

However, implementing translational and evidence-based medicine has turned out to be more difficult than we predicted. For example, the randomized clinical trial is considered the gold standard of EBM as opposed to an observational study. Yet, as Solomon quotes, "empirical proof that observational studies of treatment are wildly off the mark has been surprising elusive" [5].

> It needs to be shown empirically that the general use of evidence-based medicine in clinical decision making results in improved outcomes for patients. That is, it needs to be shown that using systematic evidence reviews, and the clinical guidelines based on them in patient care, produces better results [5].

There exists a trust-gap in the public's view of medicine, due in no small part to difficulties in replicating EBM data and a naïve reporting of "evidence" in the media without the context which other evidentiary tools such as "intuition" provide.

> To claim to be a scientist in our culture is to stake out authority and power. But physicians suffer the ill effects of this hubris: as patients and as citizens, we expect them to be far more certain than either their practice or the biology on which it is based can warrant, and for many reasons, they are likely to take these expectations for their own [1].

Western culture likes to insist on the scientific basis of medicine, and physicians often acquiesce because of our "hubris," and patient expectations. Evidence based and translational medicine are crucial, but they are slow and advance haltingly. The patient expects more than the tool can deliver.

The final mode of medical knowledge application calls itself narrative medicine. "Its central claim is that attention to narrative – in the form of… a story co-constructed by patient and physician – is essential for patient care" [5]. At its best, narrative medicine moves beyond platitudes regarding the value of listening to patients, and insists that "narrative form contains information that is relevant to

treating the individual patient" [5]. We shall see later in this chapter the power and the pitfalls of the idea that "good readers make good doctors" [6].

Ancient Greek practical wisdom and intuition, expert consensus, evidence-based medicine, and narrative constitute the tools of medical knowledge. Our medical training and practice has introduced clinicians to these tools, even if not always acknowledging them explicitly. The tools were developed in historical succession, but are not applied in a value hierarchy. Solomon advocates for using these various tools of medical knowledge in an "untidy pluralism" and practicing clinicians will empathize with this approach. Most practicing clinicians will be able to identify their use and contribution to the care of the patient, sometimes all in single encounter! But how best to become more explicit in our use of these tools in clinical medicine? The following sections of this chapter aim to explore the potential of these tools in real situations in order to assist the practicing clinician.

Induction and Reductionism

My patient has a cough, fever, and crackles at the left lung base. The chest radiograph shows an infiltrate. "You have pneumonia," I tell him. "The Thoracic Society guidelines recommend a macrolide antibiotic to cover for Streptococcus pneumoniae and atypicals. Here is your prescription…"

"But doc, how do you know I will get better? I don't feel well. My grandmother died of pneumonia and she was given the exact same prescription."

Such questions often draw empathetic platitudes, or perhaps a discussion of clinical trials if time allows. But the real answers strike at the core of what we do as physicians, and reflect on the troubled relationship of medicine to society. We are not taught to provide comprehensive answers to questions of why we do what we do. Yet this communication gap undermines the trust that "is essential to patients in their willingness to submit to treatment" [7].

We practice medicine in certain ways because we have seen them work, and because we have read about them working—in "the literature"—but do we know why we trust our experience and our studies? The instinctive reaction to cite studies does not really explain why *your* patient should trust his or her life to *those* studies. Studies simply aggregate many cases of a similar disease in sophisticated "evidence-based" ways. "What does that study have to do with me?" asks the astute patient. The question is as old as civilization itself, and one that Aristotle pondered in his discussions of "primitives," or individual cases, in the context of making a general conclusion (see Table 20.2).

Table 20.2 Medical application of Induction

Induction
Drawing conclusions about the general case from examining numerous particular instances

> Now some think that because one must understand the primitives there is no understanding at all... for it is impossible to go through infinitely many things [4].

We cannot ever review every single individual example of a phenomenon because there will always be another one that occurs in the future. Even looking at something as simple as a falling object which demonstrates the effects of gravity, how do we know that the next heavy object will fall just as the last one did? Trying to review "infinitely many things" raises the fundamental philosophical question of *induction*, or drawing conclusions about the general case from examining numerous particular instances. We make a leap, from the individual to the general. In Aristotle's world, without scientific investigation, this leap was derived from tradition, and required the use of "*phronesis*" or practical wisdom. Much of current medical practice continues to rely on practical wisdom in a way that Aristotle would recognize. After all, most of medical practice is still not "evidence-based."

However, we also believe that pneumonia will improve with azithromycin because we believe that induction works. After studying many cases of pneumonia, we can make a prediction about a future case of pneumonia. The statement sounds fairly bland when put this simply, but actually reflects a fundamental leap in philosophical reasoning that we often take for granted as medical providers, and that our patients may not deeply understand.

David Hume, the eighteenth century philosopher, reacted to the entire tenuous edifice of pre-scientific thought by introducing a deep skepticism towards causation and inductive knowledge. He realized that the attempts to explain scientific facts by appeals to phenomena such as "the humors" were fruitless and prone to error. There was no logical connection between the conclusions and the supposed facts given to reach those conclusions. For Hume, humans are left only with our experience of an event that we use as a "reason" to justify a conclusion about what caused it.

"Causes and effects are discoverable, not by reason but by experience…" Hume realized. And based on our experience, we expect the "future to be conformable to the past" [8]. However, without some theory, or rational explanation, behind our investigations, we have no basis beyond experience to predict the future. And experience can be a fickle master as he demonstrates in his famous quote about fresh eggs:

> Nothing so alike as eggs; yet no one, on account of this appearing similarity expects the same taste and relish in all of them [8].

Patients frequently commit the error of equating their experience with causation. With a little reflection, we see that we all do so. A perfect example is the patient worried about azithromycin because his grandmother received that medication and died. He thinks that the death was caused by the azithromycin whereas the true "cause" of her death was likely far more complex.

The philosophy of *logical positivism* developed to show how observational evidence could provide genuine support for a scientific theory, i.e. how "experience" could teach us about real causation. Hans Reichenbach in the early twentieth century introduced the idea of the wager, or the odds of an induction being true. We justify our use of induction by arguing that if there is *any* reliable method of predicting the future on the basis of the past, induction is it.

> Hume demanded too much when he wanted for a justification of the inductive inference a proof that his conclusion is true. What his objections demonstrate is only that such a proof cannot be given. We do not perform, however, an inductive inference with the pretension of obtaining a true statement. What we obtain is a wager; and it is the best wager we can lay because it corresponds to a procedure [8]. See Table 20.3.

The positivists abandoned the idea of objective *truth* behind scientific knowledge in favor of simply reproducible explanation. They claim that we do not have to worry about philosophical concepts causing others; we just need to be confident in the conclusions that we reach. And certainly much of day-to-day medical advice and treatment reflects this loss: "I don't know why this works, or what is going on in the body, but studies show that it does." The positivists represent a form of *empirical* thought which posits that the only source of knowledge is experience. Basic science with its biological mechanisms may supply the rationale for conducting a randomized trial, but the trial itself reflects pure logical positivism: only the observations of outcome count and can be used to guide patient care. Evidence-based medicine (EBM) does not concern itself with mechanisms of action or causation in any form; it simply reports on aggregations of massive numbers of individual *empirical* observations.

Unfortunately, empiricist explanations are often not very satisfying, especially for patients and their families who want real explanations of what is happening to their bodies. There is a human need to know "why" things happen in the world, and nowhere more so than in the body. Patients almost always want a picture, or a diagram that depicts an explanation of what process is occurring; they are not satisfied with being presented with a table of statistics. Even as EBM has provided us with the tools for the best available medical diagnosis and treatment, it has not provided the best means of engaging patients with those tools (see Tables 20.4 and 20.5).

Modern medicine has made its most spectacular advances applying empirical observation to ever smaller biological processes by isolating single variables and testing them. This is known as "reductionism" and it is the opposite of holism which asserts that certain knowledge requires studying intact systems. Reductionism works by breaking down biological systems into component molecular interactions, such as we do in pharmacological research. Holism requires the opposite approach,

Table 20.3 Philosophical Concept of Knowledge

Empiricism
The only source of knowledge is experience, rather than reasoning from principles

Table 20.4 Modern Approach to Scientific Method

Reductionism
Breaking down biological systems into component parts in order to test them

Table 20.5 Evolving Approach to Scientific Method

Holism
The sum of a process may be more than its component parts

positing that the sum of a process may be more than its constituent parts. Some research is done in holistic medicine, such as looking at how patient attitude affects cancer outcomes. Holism is underpinned by the concept that there is a link between our physical health and our more general 'well-being'. Unfortunately, such holistic care is often very difficult to implement in practice and can quickly become full of platitudes rather than concrete pathways to improve health. Because of the difficulty in implementation, complex questions of how attitude or prayer might affect cancer outcomes is left to the "art of medicine."

Contemporary philosophers such as Thomas Nagel question whether further scientific advances will require studying whole systems rather than just parts. Extremely complex systems, such as the human brain, may have a whole that is greater than the sum of their parts. Nagel does not see reductionism as satisfactory for explaining the operation of the mind; neuroscience can tell us how molecules cause nerves to fire, but not how consciousness is created.

> The existence of consciousness seems to imply that the physical description of the universe, in spite of its richness and explanatory power, is only part of the truth [9].

If physical processes cannot account for consciousness, then the physical description of the body may not be adequate to account for its complete development, and that may have implications for descriptions of evolution that describe only changes in physical processes of living things. For modern scientific medicine, the physical description of the body is what we rely on implicitly, and everything else is compartmentalized as "bedside manner."

Nagel's critique goes on to show that the existence of mind challenges Darwinian "blind" evolution. According to Nagel, only if there exists some teleology, or intrinsic destination, for evolution can one explain the emergence of consciousness.

> To explain consciousness, a physical evolutionary history would have to show why it was likely that organisms of the kind that have consciousness would arise… There [might be] natural teleological laws governing the development of organization over time, in addition to laws of the familiar kind governing the behavior of the elements [9].

Patients facing serious illness or death often find comfort in the idea that their lives have meaning—even if it is not always religious meaning. The holistic consciousness that Nagel describes is currently scientifically inaccessible to us. Will humanity's yearning to be seen as more than a collection of parts always remain at the level of clinical art, or could it emerge in a scientific manner and become amenable to reproducible study? Will the line between the "art" of medicine and the "science" always remain drawn where it is now?

As our culture becomes increasingly diverse and skeptical of claims about "truth," a working familiarity with the philosophy of science becomes helpful to medical providers. Scientific medicine is openly debated in the marketplace of ideas now more than ever. Every one of my patients wonders whether they should be seeing me rather than the *curandera*, the naturopath, or Google. And if they do see me, they wonder if I know what I am doing, and why they should trust me with their lives. And these are good questions, ones that we should embrace because they deserve answers rather than trite statements like, "Because this is how I was

trained." In the next section we will look at ways that medicine with its reductionism can still manage to embrace the holism of the patient's entire situation through narrative.

Narrative Medicine and Narrative Fallacy

Here is a patient history taken while admitting from the emergency department to the hospital:

> HISTORY OF PRESENT ILLNESS: Mr. B is a very pleasant 60-year-old male with extensive past medical history who presented for evaluation of extreme weakness. The ambulance reports that the patient had a witnessed fall while walking to the store to purchase some cigarettes. He states that he is currently homeless, but compliant with medications and follow-up with the clinic. He did not report any syncopal episodes, or chest pain, but does report significant shortness of breath.

It's just the beginning of a story really, or perhaps the end of a long and complex story of a difficult life. Like any story, it conceals as much as it reveals, and creates a mystery. But the snippet already lets the doctor start sifting through medical possibilities, thinking of other questions to ask, or tests to run.

The focus on the patient's story has led to the modern methodology of "narrative medicine" as a means of creating medical knowledge about a patient. Narrative medicine is nothing new of course; the doctor's job has always been to listen to the patient and to be a witness, and to show empathy by somehow connecting to the story that the patient tells. Even the most technical of the subspecialties listen to patient stories: surgeons, electrophysiologists, and interventional radiologists. And those of us in more holistic specialties have made this our bread and butter. For better or worse, doctors are often evaluated by patients nearly entirely based on our ability to listen and empathize.

Stories allow the clinician to make sense of particularities and match them to patterns. "The experience of narrative is conditioned by *schemas*; that is, narrative has a recognizable structure that governs recognizable features so that, in a manner very different from positive science, we *notice* what is not there along with what is there" [10]. The following history demonstrates our ability to quickly fit a story into a schema and fill in the blanks for what elements are present or missing:

> HISTORY OF PRESENT ILLNESS: Mr. X is a 70-year-old man without known cardiac history who was transferred here for management of ventricular fibrillation arrest. This morning the patient was loading boxes into a truck and went back into the house. His daughter heard a crash and found the patient on the floor, unconscious and unresponsive. The history was obtained from the patient's family and daughter who lives with him. Per brother's report, patient had been complaining of left shoulder pain for the last few weeks. He does not seek medical attention and has not seen a doctor for many years. Apparently 5 years ago he saw any eye doctor who told him that he needed to see a primary care physician based on the findings in his eyes."

Mr. X has suffered from significant vascular disease for years, he progressed to classic angina and then suffered a massive infarction while loading boxes. In this

case, Mr. X does not tell his own story. In fact, in some sense, none of us may *ever* tell our own stories. People use the cultural baggage that they inherit in order to make sense of the events of their lives, and this "baggage" actually determines the course of the story. Nowhere is this more evident than in medicine. We are a culture currently obsessed with "health" and medical advances. All my patients have filtered their health experiences through a myriad of lenses before I hear about them: grandmother's herbal tea, House MD, and so many others. We all tell filtered stories, and the physician's job is to be the literary critic and detective.

Taking relatively undifferentiated symptoms, and pre-conceived notions, and weaving these into a medical story is the skill that distinguishes a master clinician. At its best, it is what makes primary care and hospital medicine so exciting because nowhere else are we exposed to raw stories prior some other clinician's interpretation.

> If we wish to know about a man, we ask "what is his story - his real, inmost story?" - for each of us is a biography, a story. Each of us is a singular narrative, which is constructed, continually, unconsciously, by, through, and in us [11].

When I have medical students on my service, we often spend time reviewing pathophysiology, but even more time may be spent teaching how to construct the patient's story. Medical students quickly learn to assemble "facts," such as blood pressure, symptoms and lab values. But not until they start to create a plausible narrative with the facts do they become doctors. Sometimes this is called the art of medicine, as opposed to science, but it is also true that "scientific reasoning often makes use of causal narratives" [5]. In some ways, doctors function as the close readers of the "book" of the patient's story, matching patterns against what we have already read and know.

Narrative medicine has pointed out the distinction between the chief complaint and the patient's chief concern. "That concern is the patient's awareness of what his illness means in relation to the ongoing story of his life" [10]. The clinician constructs a story, and the patient also constructs a story, but sometimes with a different plot. This process has been called "re-storying" in which the clinician translates the patient's narrative into a medically conditioned narrative. The patient has "chest pain," and after tests the clinician reframes the story by telling the patient that she has "acid reflux." For the most part, this "re-storying" has "positive therapeutic effects," [10] but can lead to problems. The stories the patient tells, and then the ones we tell, do not always harmonize with actual events. Even more concerning are the selective memories that we hear every day, the downplaying of drug use, and the dissembling in order not to alarm family members.

> Humans are… in general susceptible to the 'narrative fallacy' in which the attempt to weave experience into a coherent story results in the omission of facts, or even in their (intentional or unintentional) distortion or fabrication [5].

Doctors are not immune to the narrative fallacy. In fact, in order to 'package' a patient into a "History and Physical," "Progress Note," or one of the other codified narratives that physicians use for communication, we are *required* to commit the narrative fallacy by assigning a diagnosis. We cannot complete a patient assessment

of any kind without constructing a story. And the story must fit one of the accepted and routinized narratives that scientific medicine has constructed in its repertoire. In other words, we have to assign one or more diagnoses, and these diagnoses are always the conclusion of the story that we construct (Table 20.2).

This narrative urge ties directly to the case-based, practical, knowledge of the doctor. Physicians are not scientists, we are a humanistic profession and would starve without a constant diet of stories. However, perhaps not all illnesses *should* fit a narrative. Chaos and its acknowledgement might serve medicine's interest from time to time. We shall address this issue again later when we take up the question of medical knowledge in its larger social context.

The Existential Encounter

Existential philosophy begins with the assertion that the autonomous individual has the capacity, and indeed the obligation, to self-reflect and create a meaningful existence. In popular culture we know this as the "existential crisis," when someone questions the purpose or value of their life. Hospitalized patients nearly always undergo an existential crisis due to the gravity of an illness that requires an inpatient stay. The patient confronts the reality of illness and no intellectual reasoning can soften the blow. Meanwhile, the doctor braves the responsibility for another human's life, and no amount of training can lighten that burden.

Hospitalization for the patient with emphysema who has been a long time smoker nearly always occasions a profound introspection into the choices they have made in the past, and the amount of life they have left to them. No longer do we hospitalize the worried-well. As inpatient acuity rises amongst our patients, so does the potential for a confrontation with mortality. For the doctor, the patient's existential moment often passes unnoticed in our busy day. Rita Charon, in *Narrative Medicine*, remarks on this by lamenting, "If only the doctor would, as a matter of routine, be prepared for the jarring, jolting, inarticulate presence of dread; if only he would be attuned to the inevitable and exorbitant terrors that illness brings [6]."

Existential philosophers nearly always begin with an acknowledgement of dread, and none more so than the first existentialist, Soren Kierkegaard. His 1849 essay, *The Sickness Unto Death*, begins by asking, "Is despair a merit or a defect?" [12]. Yet, how can despair be a merit, or an asset? Kierkegaard's prose is notoriously convoluted and difficult, often itself causing despair in the reader! The process of teasing out his meaning may help us better understand patient crises when faced with hospitalization.

> In despairing over something, he really despaired over himself, and now he wants to be rid of himself [12].

Despair is complex, and linked to our self-regard. Most hospitalists attend to numerous patients with imminently terminal diagnoses, either arranging hospice at home upon discharge, or assisting with actual symptom management for their final

few breaths. Are dying patients in despair? And if they are, is this a "merit or a defect?" Or perhaps the essay refers to the physician's own existential predicament as we face our inability to perform our duty to heal? Most dying patients seem inexplicably at peace, whereas their families and clinicians are clearly despairing.

> Thus to be sick unto death is to be unable to die, yet not as if there were hope of life; no, the hopelessness is that there is not even the ultimate hope, death [12].

What is the relationship between despair, hope and death? These concepts lie at the root of the existential crisis entailed by hospital stays. Kierkegaard refers of course to the Christian faith of physical death not signifying ultimate death, that in fact physical death is the ultimate hope of heaven. But the essay also refers to an earthly despair as well, "there is not one single living human being who does not despair a little, who does not harbor an unrest, an inner strife" [12]. I have seen patients sick unto death even as they were young and quite alive.

My hospital is on the front lines of America's heroin epidemic, and if there is any substance that manifests Kierkegaardian despair, it is heroin. Once I cared for a 30 -year-old woman who arrived in the emergency department with a fever of 103, rigors and pinpoint pupils. Her body hurt "all over," but mostly when she took a breath, when the pain radiated to the middle of her upper back. Her left forearm had needle tracks with a palpable corded vein where the poison had clotted and scarred injection sites. There is a wild look in heroin eyes that radiates despair.

The reader knows how this story proceeds, for it is a Greek tragedy with its ending foretold before the story even begins. The "heroine" has a fatal flaw. A heart valve infection from dirty needles and dirty drugs—right sided endocarditis with septic pulmonary emboli. Blood cultures with Staphylococcus aureus. Homeless. A "boyfriend" who brings a backpack to her hospital room and spends a lot of time in the bathroom. The standard of treatment for this woman would be intravenous antibiotics for weeks; we used to recommend six. But the logistics of that are impossible. How to maintain an IV line in someone who would rather use it as access for the next high? How to deliver medications at home when there is no home? Various infectious disease studies have experimented with a shorter treatment course, down to even 2 weeks of IV antibiotics. Even this will be nearly impossible for her to accomplish.

The addict lives entirely for the moment and cannot conceive of tomorrow, much less 2 weeks from now. Just 2 months ago she delivered a baby, could not stay clean, and lost her infant to state protective services. If she could not stay clean for her own baby, how will she do so for a mere life-threatening blood infection? My patient has no hope for life, nor even for death, because she cannot conceive even of death. When I talk about "life threatening," her eyes wander to the window. She has no conception of any future. And without the ultimate hope of death, she is truly in despair, without even the benefits of despairing, and thereby perhaps changing her life.

> Not to be in despair must signify the destroyed possibility of being able to be in despair; if a person is truly not to be in despair, he must at every moment destroy the possibility [12].

Existential despair links intimately to our conception of time. A patient arrives in the emergency department not breathing well. The hospitalist takes the history. We try to match the patient's perception of when various symptoms occurred with

our natural history of congestive heart failure. The patient's recitation of the events has to match the timeline of medical knowledge for that condition. When the dyspnea "just came on" the doctor thinks pulmonary embolism, but when "it has been a while" we think pneumonia if it has been a medium amount of time and heart failure for a longer course. Every clinician has experienced the dissonance when the related amount of time and what we hear suffers through an assumption (Table 20.6).

Patients have their own internal time through which they make sense of their symptoms and illness recognizable as two time horizons (see Table 20.7). First is the immediate, the "now." Pain brings one into the present moment like nothing else. Right now I feel like this, and I want to feel better. The second timeline corresponds to personal destiny; how does this illness fit into the meaning of my life? The individual life meaning depends on where one sees it is headed. What is the destination of my life and what impact does illness have on that? The belief in purpose, goal, or cause is described as *teleology* (see Table 20.6). Breast cancer survivors have best highlighted how patients find meaning in their disease in modern culture, and thereby create the teleological nature of "illness time":

> Writing in a journal, even for 15 minutes a day, helped me explore my feelings and find meaning in my cancer experience.

> I am so grateful I was given a second chance – even a third chance at life. Just having a strong need to be there for my daughters, family, friends and loved ones… really got me through it. It's not about me. I'm not the only person in this fight [13].

Illness has meaning, and that meaning becomes defined by the place where the illness takes you. Breast cancer advocacy networks and support groups have been the most active in promoting the discovery of meaning in illness, but everyone creates signification with even minor illnesses: "I was working too hard, so now I got this cold and I'm going to have to slow down for a while."

The physician–patient relationship plays out between the two time horizons of illness: the "now" of suffering, and the teleology of human destiny. Each patient conceives of medical treatment in terms of his or her philosophy of destiny. "What good will come of medical treatment," is a question that has meaning only with knowledge of one's end. "What is my purpose on earth," has to be answered before one can answer the question of what therapy to undertake. For example, a routine knee replacement makes sense in the context of being able to achieve mobility and meaningful activities. Without the horizon of a personal destiny that requires a

Table 20.6 Assigning Meaning to an Illness

Teleology
The attempt to describe things in terms of their apparent purpose or goal

Table 20.7 Patient's Internalized Time Perception of their Illness

The time horizons of illness
The "now" of my suffering
The teleology of my destiny

workable knee, replacing it has no meaning. Some patients' beliefs require that they stay in a wheelchair, others require peak athletic performance. Of course, the immediate time horizon of suffering may also come into play. End-stage arthritis is painful, moment to moment, and every moment of every day. So the patient makes his or her decision about knee arthroplasty between the two poles of immediate suffering and the long-term destiny. Knee replacement as a medical therapy is a simple example that allows us to see these two poles, but indeed all medical interactions revolve around these same two understandings of time.

Edmund Husserl, existentialist philosopher of human perception, described these two horizons of time:

> There belongs to every external perception its reference from the 'genuinely perceived' sides of the object of perception to the sides 'also meant' – not yet perceived but anticipated [14].

Perception of the moment of "now" occurs always with our anticipation of a similar past and future experience. The experience of pain now is always informed by the past and where we are headed in the future. Think only of the patient with appendicitis. After diagnosis and prior to surgery, the patient is often stoic in the face of pain, anticipating its imminent resolution. But post-operatively, after realizing that surgery did not resolve all the pain, and with no expectation of impending relief, the same pain takes on an entirely different character.

Classical thought, both philosophy and theology, all presupposed an implicit human teleology. Aristotle proposed perfecting human virtues as our end goal; Christian theologians turned towards completing God's will on earth. Only with Darwin and evolutionary theory did our Western culture lose its implicit teleological character. Current biological theory posits that no creatures are being "perfected," but only increasingly adapted to their environments. Humans are not the "peak" of evolution, which teleology would maintain, but are only one of evolution's branches, subject to the forces of nature and reproduction like everything else. And yet as doctors, we strive mightily against the bonds of evolution by fighting to prevent patients from falling prey to its ravages. We battle against genetic defects, risk factors, and even social Darwinism in its placement of some patients into unhealthy living situations. The very existence of the doctor is a daily poke in the eye of blind evolution. And as we battle the genetic and social determinants of evolution, we are often unwitting proponents of a teleological view.

And as patients, why seek care if there is no future? Kierkegaard's dark essay may actually be about light. The possibility of despair may be essential to the human endeavor of hope. The sickness unto death has a double meaning. Cancer and heart failure are sicknesses unto death, but so is the loss of despair. To "despair" is precisely to act in accordance with the facts, to give up an attempt *because* the goal is impossible. The patient requires an acknowledgement of despair in order to come to terms with the illness and thereby, perhaps, to have hope. The heroin addict who talks of "discharge tonight" because she has "things to do" has moved too quickly to hope without going through appropriate despair. The heroin addict who looks out the window while discussing a heart valve infection has never moved past despair at all to encounter the possibility of hope beyond it.

The physician often needs to recreate teleology, or the meaning of the illness, for therapy to succeed. It is a task that neither physicians nor patients are well-trained to undertake. Except for hospice patients who have perfected it. The formula for all despair is to "want to be rid of oneself." The addict despairs in this sense. But the hospice patient has accepted despair and thereby rid himself of it because he no longer wants to be rid of himself, and has finally, and perhaps for the first time in his life, accepted himself.

Philosophy opens a door for us to see how hospitalized patients encounter an existential dilemma. This crisis engenders a reckoning with the dualistic nature of "illness time," both the immediate now, and the teleological future. Physicians help patients by interpreting their "despair" in the face of illness in terms of their ultimate destinies as individual humans.

A Systems Perspective on Medical Knowledge

Physicians encounter patients exclusively one at a time. Our decision-making, the use of our knowledge tools, and even our existential dilemmas all take place in a context of a single patient. But our roles as hospitalists extend far beyond individual patients out to our hospital team, our community and our society. Hospitalists more than any other specialty explicitly function within a larger "team" structure. How does this social role affect how we apply medical knowledge?

Understanding a medical encounter as a narrative, as we have seen, entails an entanglement with meaning and with a goal of care. Because of the concern about "good" and "bad" outcomes of stories, they inevitably lead to questions of ethics: what is a good outcome? Every medical narrative we read has an ethical subtext as both the physician and the patient ponder the goal and weigh it morally. Modern medical ethics "has primarily been dominated by applying certain analytic principles to ethical situations: autonomy, beneficence, nonmalfeasance, and justice" [10]. These principles help us to make decisions for and with patients. They are fairly easily taught and have served practicing clinicians well. At their best, these principles can be used to help a patient address their personal *chief concern* and achieve their own highest good (see Table 20.8).

However, a principle-based ethical system is difficult to apply to physicians ourselves while we work and care for patients. What does it tell us about achieving our "highest good" in being a doctor? Aristotle used a different ethical system which we now call "virtue ethics." His writings promote ethical behavior as virtuous behavior, and consists of those actions that enable each person to achieve their own *eudaimonia*, or "highest good" (see Table 20.9). Virtue was defined as that which leads to a good life, and were listed by Aristotle as competency, conscientiousness, discernment, compassion, trustworthiness, and decency. The crucial point of virtue ethics is that one cannot define what actions those excellences would lead to without knowing one's community. What are proper behaviors towards others? Well, what is your tribe or group? What is the good life? Again, tell me about your community.

In a multicultural society, answering questions about community has often created a roadblock to using virtue ethics. Although few would argue with the list of virtues, coming from any culture, the actions those virtues require vary considerably. Within any particular group, the virtues are used to what is a "good" person, and hospitalists have become just such a community. More and more, hospitalists work within integrated health systems, whether private, non-profit, or governmental. These health systems function in some ways like the old Athenian city-state. They are culturally homogenous because modern medicine has defined proper behavior. They are democratic and egalitarian as every team member contributes to best patient care. And finally, they are defined in terms of ultimate goals: healing patients. These ultimate goals become more explicit every year as health systems take on "risk" through bundled payments, accountable care organizations or other payment models. With risk-based payment comes an inevitable focus on outcomes and defining the "good" in life (Table 20.10).

As we move into a city-state form of integrated medical care, the use of virtue to help guide us may become more helpful:

> Virtue ethics – conceived in terms of the narrative knowledge and narrative skill of repeatedly relating part to whole – signals the necessity for a "pause" in action to ask about conscientiousness, discernment, compassion, and overall decent behavior in the face of suffering [10].

Each integrated health system will define *eudaimonia* differently. This consideration takes the form of "relating the part to the whole." Consider the patient with new atrial fibrillation. She was admitted from the emergency department, short of

Table 20.8 Principles of Decision Making

Principle-based ethics
Autonomy
Beneficence
Nonmalfeasance
Justice
Virtue-based ethics
Competency
Conscientiousness
Discernment
Compassion
Trustworthiness
Decency

Table 20.9 Philosophical Goal of Care

Eudaimonia
A contented state of being happy

Table 20.10 Risk of Determining Good Outcomes

Narrative fallacy
The attempt to weave experience into a coherent story resulting in distortion

breath and with a racing heart. Her EKG confirmed atrial fibrillation so she came to the telemetry floor on a diltiazem drip which slowed her heart rate from 150 down to around 100. On further exploration of her history she had been having episodes like this for the past few months, all resolving spontaneously until now. Her echo showed some left atrial enlargement, and she was concerned that her heart "was betraying her." We discussed rate versus rhythm control, stroke risks and what ongoing care and follow-up she would need.

The multiple questions regarding what is best for my patient are informed by scientific evidence, but do not end there. This woman will need to continue to see medical providers and the next step in her care will involve conversations with her regarding her activity goals, her stroke risk, and her home situation. How confident am I in her follow-up with a primary care provider? The answer to this last question will likely depend on the relationships between primary care and cardiology, and both of those tied into payor source. Whatever medical "good" we can offer her is complicated by a myriad of factors that have to do with the physician's skill as a clinician, the depth of the physician–patient relationship, and their role in the larger society.

Inside my health system, the *telos* for patients is quite clear, and in fact summarized in its mission statement: "Care you can have faith in." Like all health systems, we strive to provide a continuum of care with the goal of maximizing our patients' health. Every day, staff show up to work and assume their shared place in our common city-state, subsuming our outside roles to our shared *telos* of the patient "good." And because we share a common end-goal for patients, the physician's practical wisdom comes back into play. We can use our intellectual wisdom, combine it with our practical wisdom, as we make diagnoses and implement treatments that are scientifically based but individually tailored to each specific person in his or her context. The rest of my culture is fragmented in the post-modern world, but at work the classical model of virtue ethics harmonizes actions, day after day.

We must all ask ourselves how our health systems define *eudaimonia*, the good life, and how we think of patients' teleology, or goal in life and illness. How does your health system define *eudaimonia*, and how does that affect what you do day to day? Attempting to discharge the patient with endocarditis and addiction issues, who needs long-term intravenous antibiotics, but has a poor or dangerous living situation, is a constant challenge. How much "social engineering" are health systems willing to perform in order to achieve better health outcomes for their at-risk patients? Does our responsibility stop with providing the antibiotics, or does acting virtuously require providing addiction treatment? How will we integrate patient responsibility in to our care plans when there is a financial risk for our health system, or eventually even for us personally as providers?

On the patient side of the health system interaction, can we employ virtue ethics to recapture patient responsibility? The virtues for physicians reflect a corresponding list for patients. Surely we can hope for more in our patients today than simply that they are "autonomous." My patient with endocarditis survived her initial bout despite receiving less than ideal antibiotic therapy. For months I saw her and her boyfriend bounce between the emergency department, the inpatient unit, and the

hospital cafeteria. Once, as I left my late shift at 2 am, her boyfriend was pushing her down the street about a block from the hospital in a wheelchair labeled "hospital property." My hospital has become her "community" in some odd codependent way. And as her community, perhaps her only community, there may be a place for her to act virtuously. I often propose nursing assistant or nursing school to our "frequent flyer" patients; health care could benefit from their perspective and they could benefit from the discipline and organization we offer.

As the above nearly daily patient care conundrums indicate, accomplishing the healing task of medicine in complex modern environments is not clear-cut. In fact, creating something coherent out of the complex lives and social situations of many patients often seems impossible. And perhaps it indeed is. Earlier we discussed narrative medicine and the narrative fallacy of insisting the all patient stories fit into a recognizable "plot." The promise of virtue ethics offers an analogous situation in a social context: sometimes patient situations represent pure chaos. Patients and their "biopsychosocial" story make less and less "sense" within our societal health system. The heroin addict with endocarditis and the elderly woman with no family, no treatable medical conditions, but increasing inability to care for herself at home, both have no virtuous pathways today. The virtuous physician simply cannot act with Aristotle's commendable attributes of compassion, trustworthiness and discernment. Of what use is discernment within a maelstrom of chaos? Sometimes an acknowledgement of chaos may be its best antidote. We may come to see that the lack of a virtuous pathway in our day to day jobs may actually be the main factor contributing to physician burnout. There seems to be a fundamental human need to be able to see ourselves as acting virtuously within our group or society.

The narrative structure of the physician–patient relationship, which starts with practical and then scientific knowledge, necessarily leads to a concern with outcomes and goals. These chief concerns open the door to the inevitability of an ethics to everything that the provider does. We are trained to use principle-based ethics, but may find that our place in integrated health systems allows us to use virtue ethics as well. The new perspective of virtue ethics may allow us to gain perspective on care decisions, and possibly even help our patients to cultivate virtue in their own lives.

Conclusion

This chapter has attempted to highlight how clinicians use medical knowledge in clinical care. We reviewed how medical training develops practical wisdom along with more "scientific" evidence-based tools, and then culminates in narrative techniques which allow us to confront the existential dilemma of the individual patient encounter. Finally, we concluded with the expansion of single patient encounters to include the hospitalist's role in a health system in order to shed light on how virtue ethics assist in patient care.

Throughout this chapter we have encountered ideas from major philosophers including Aristotle, Hume, Kant, Kierkegaard, Husserl, and Nagel. The actual practice of modern medicine stems from their insights in ways we often do not appreciate as we become caught up in the pressing affairs of patient care. Reflexively, providers' daily duties also cast light on these philosophical ideals. Physicians are also philosophers, and our intensely personal work within a moral system, with the goal of improving humanity, is one that would resonate with Aristotle two millennia later. To be a physician is necessarily to be a humanist, and a philosopher.

The refinement of virtue can inspire both patient and physician to confront their existential predicaments and confront "despair." Burned out clinicians and burned out patients both stem from a loss of imagining virtuous actions within existential moments. Can we create pathways for virtue for ourselves and for our patients in the often chaotic environment of healthcare? This chapter advances the argument that practical philosophy, and the humanities, are important in the clinical practice of medicine. That is, they are not just about better communication, or the physician–patient relationship, but affect actual patient outcomes because *how* we apply our tools of knowledge determines the types of outcomes that are even possible, even when those outcomes are sometimes only chaos.

Just as humanism is integral to medicine, so is being a human integral to being a physician. Practical wisdom and intuition begin with fundamentally human ways of knowing, not unique to providers. To be a doctor is to be human, to be human is to be a doctor. All humans are physicians as they try to improve the lives of those around them; the secret for each of us is to know our own specialty and thereby our limits.

References

1. Montgomery K. How doctors think: clinical judgment and the practice of medicine. New York: Oxford University Press; 2006.
2. Bynum W. The history of medicine: a very short introduction. Oxford: Oxford University Press; 2008.
3. Braude H. Intuition in medicine: a philosophical defense of clinical reasoning. Chicago, IL: University of Chicago Press; 2012.
4. Aristotle. Posterior analytics. In: McGrew TJ, editors. Philosophy of science: an historical anthology. Chichester: Wiley-Blackwell; 2009. p. 46.
5. Solomon M. Making medical knowledge. Oxford: Oxford University Press; 2015.
6. Charon R. Narrative medicine: honoring the stories of illness. New York, NY: Oxford University Press; 2006.
7. Jacobs AK, American Heart Association. Rebuilding an enduring trust in medicine: a global mandate: presidential address American Heart Association Scientific Sessions 2004. Circulation. 2005;111(25):3494–8. Print.
8. TJ MG, editor. Philosophy of science: an historical anthology. Chichester: Wiley-Blackwell; 2009. p. 220–4.
9. Nagel T. Mind and cosmos: why the materialist neo-Darwinian conception of nature is almost certainly false. New York: Oxford University Press; 2012. Print.

10. Schleifer R, Vannatta J. The chief concern of medicine: the integration of the medical humanities and narrative knowledge into medical practices. Ann Arbor, MI: University of Michigan Press; 2013.
11. Sacks, Oliver, 1933–2015. The man who mistook his wife for a hat and other clinical tales. New York: Summit Books; 1985.
12. Kierkegaard S. The sickness unto death. London, New York: Penguin; 2008.
13. Metastatic Breast Cancer Network [Internet]. New York; 2004. Available from: www.mbcn.org/stories. Accessed 5 Jan 2017.
14. Welton D, editor. The essential Husserl: basic writings in transcendental phenomenology. Bloomberg: Indiana University Press; 1999.

Further Reading

Devettere R. Practical decision making in healthcare ethics: cases and concepts. 3rd ed: Georgetown University Press; 2009.

Index

K. Conrad (ed.), *Clinical Approaches to Hospital Medicine*,
https://doi.org/10.1007/978-3-319-64774-6