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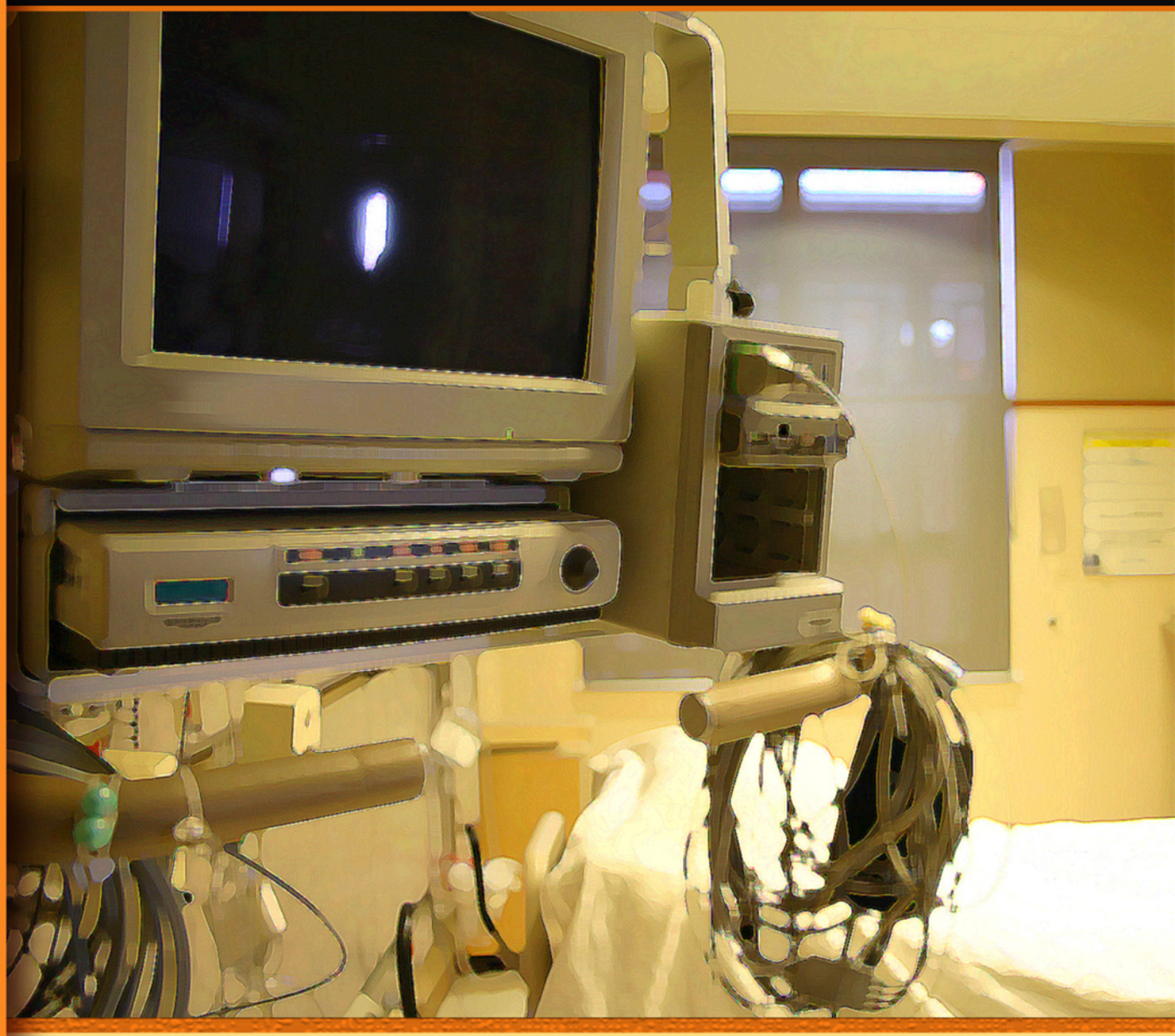

Challenges in Acute Geriatric Care

Jochanan E. Naschitz
Editor

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2009. ISBN 978-1-60741-309-7

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Nova Biomedical Books
New York

Library of Congress Cataloging-in-Publication Data

Challenges in acute geriatric care / [edited by] Jochanan E. Naschitz.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-60876-403-7 (E-Book)
1. Geriatrics. 2. Geriatrics--Case studies. I. Naschitz, Jochanan E. [DNLM: 1. Geriatrics. 2. Chronic Disease--therapy. 3. Physician-Patient Relations. 4. Signs and Symptoms. WT 100 C4373 2009] RC952.5.C43 2009 618.97--dc22
2009006346

Published by Nova Science Publishers, Inc. ✦ New York

Dedication

To Vera, the better self of mine

Contents

Preface

Hospitalization is the proverbial 'double-edged sword' for elderly patients. On the one hand, it offers them benefits from specialist consultation and advanced medical technology. On the other hand, it subjects them to risks of iatrogenic illness. While hospitalization is a physical and psychological challenge to the patient, the encounter with the elderly patient possibly will be challenging to the physician, in defying his skills and acumen. Indeed, the physician finds limited advice in textbooks of internal medicine or geriatrics, and can not much rely on results of randomized prospective studies, which usually recruited younger populations. Challenging can be some among the more common clinical situations if the best clinical practice is unsatisfactory. For such conditions we attempted to expose the latest evidence, define the frontiers of knowledge, and forward recent guidelines or consensus recommendations. Puzzling case histories of patients admitted to the acute geriatric ward are also presented. Though uncommon in everyday practice, such cases are stimulating and important in conveying the challenge of problem solving and, in this manner, enhancing our skills as clinicians.

The proposed work is supposed to fill a gap in the literature in presenting a collection of topics on acute geriatric care. Most chapters are structured as grand rounds, focused on clinical problems that have limited disclosure in textbooks, presented as a dialog between theory and practice, written by clinicians for clinicians. This collection is based on encounters between geriatricians and consultants, meant to resolve clinical problems; a collaboration where clinical experience and interdisciplinary exchange may supplant scanty guidelines. A multidisciplinary approach is also proposed to reduce functional decline of elderly patients, decrease length of hospital stays, and prevent nursing home admissions.

As the world's citizens become older, the more appealing becomes geriatric medicine. To those who care for the elderly is offered this book.

Jochanan E. Naschitz

In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter I

Hypertension Management in Acute Geriatric Care

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Blood pressure (BP) control is often impaired in elderly persons and may get worse during acute illness. As a result, uncontrolled hypertension or hypotension are common among patients admitted to the acute geriatric ward.

I. Hypertension in the Elderly

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure classifies arterial hypertension as a usual systolic BP of 140 mm Hg or greater or usual diastolic pressure of 90 mmHg or greater, BP levels for which the benefits of pharmacological treatment have been definitively established in randomized placebo-controlled trials [1]. The prevalence of hypertension increases markedly with age, such that approximately two thirds of persons over 60 years of age have hypertension [2]. Elderly subjects are also more likely to have white coat hypertension, pseudohypertension and postural hypotension [3]. The pattern of BP elevation changes with age [2]. Before 50 years of age, most hypertensives have elevated diastolic BP. After the age of 50 years, as systolic pressure continues to rise and diastolic pressure tends to fall, isolated systolic hypertension predominates. Diastolic BP elevation is cause by constriction and hypertrophy of smaller arteries. Systolic BP elevation is mostly caused by loss of distensibility of the larger arteries, especially the aorta [4]. Most cases of isolated systolic hypertension (systolic BP higher than 140 mm Hg and diastolic BP lower than 90 mm Hg) arise de novo after age 60 and are not 'burned-out' middle-age diastolic hypertension [5]. The risk of cardiovascular disease increases continuously with increases in systolic or diastolic BP [2], but elevated systolic BP

is more important than elevated diastolic BP as a risk factor for cardiovascular and renal disease [3]. Isolated systolic hypertension is a major risk factor for diastolic heart failure.

There is ample evidence supporting treatment of isolated systolic hypertension. In the Systolic Hypertension in the Elderly Program (SHEP) which enrolled patients with systolic BP ≥160 mm Hg and diastolic BP <90 mmHg, treatment with chlorthalidone for an average of 4.5 years resulted in impressive reductions in the incidence of stroke, coronary heart disease, and congestive heart failure, as compared with placebo [6]. In the European Trial in Systolic Hypertension and in the Systolic Hypertension in China Trial, which enrolled patients with isolated systolic hypertension, treatment with the calcium-channel blocker nitrendipine was associated with decreases in the incidence of stroke, coronary heart disease, and congestive heart failure [7,8]. These 3 trials demonstrated the benefit of antihypertensive drug treatment. A meta-analysis was performed by pooling the patients from these 3 trials with a subset of patients with isolated systolic hypertension from 5 other trials in the elderly. The pooled results of 15,693 older patients with isolated systolic hypertension prove that antihypertensive drug treatment is justified if on repeated clinic measurements SBP is 160 mm Hg or higher. This evidence has not been well incorporated into clinical practice; in up to 60% of elderly patients, hypertension remains untreated or poorly controlled [9,10].

The oldest hypertensive patients, despite worse BP control, are being treated less aggressively and with fewer medications than their younger counterparts [11]. This may be a reflection of the current controversy in treating the oldest hypertensive. The effects of treating hypertension in patients older than 80 years of age are unclear, because few studies have been performed in this age group. The Hypertension in the Very Elderly Trial enrolled subjects with an average age of 84 years. After 13 months of follow-up, subjects receiving a thiazide diuretic or lisinopril had by 53% less stroke vs patients receiving placebo; however, total mortality was 23% higher among patients receiving antihypertensive treatment [12]. A similar trend toward increased mortality with antihypertensive therapy was noticed in other small trials involving the very old [13,14]. In distinction from the former studies, the only large prospective study showed that hypertension treatment in nonagenarians is beneficial**.** 3845 patients who were 80 years of age or older and had a sustained systolic BP ≥160 mm Hg were assigned to receive either the diuretic indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting–enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg. At 2 years, the mean BP while sitting was 15.0/6.1 mm Hg lower in the active-treatment group than in the placebo group. Active treatment was associated with a 30% reduction in the rate of stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes, and a 64% reduction in the rate of heart failure [15].

Is lower BP always better in the elderly? This question has been repeatedly raised [16,17]. Myocardial perfusion takes place during diastole, and excessive reduction of diastolic BP could be detrimental in patients with coronary artery disease. Several studies have suggested that a diastolic pressure below 60 mm Hg, particularly in patients with documented coronary disease, may be associated with an increased risk of myocardial infarction and death (the so-called J-curve phenomenon) [18]. The risk of the J-curve effect might be more pronounced in the old-old. However, a meta-analysis of clinical trials indicated that the increased risk of coronary events at low diastolic BP was unrelated to

treatment or pressure levels, but was probably secondary to serious illnesses that were causing the low BP [19]. Although reducing diastolic BP to very low levels might be harmful in some cases, the overall benefits of antihypertensive therapy in patients with isolated systolic hypertension, including the reduction in coronary heart disease, are well documented [20].

There are additional points of concern. Older patients often have orthostatic hypotension that may be ignored in treating hypertension based only on measurements made when the patient is supine [21]. Indeed, a special emphasis is required for measuring BP in elderly hypertensive patients in the supine as well the seated position. Orthostatic hypotension is a major cause of morbidity and mortality elderly subjects, especially when frail [22,23]**.** Elderly patients often have decreased intravascular volume, increased arterial stiffness with impaired vasoreactivity, rendering them more susceptible to adverse effects of blood pressure–lowering medications [22,23]**.**

Furthermore, BP response to antihypertensive medications is smaller in the elderly than in similarly treated young patients [24]. In a study, the 'efficiency of treatment' was computed by plotting antihypertensive 'treatment intensity' against the proportion of patients with controlled hypertension. The 'treatment intensity' score was derived by dividing the daily dose taken by the maximum recommended daily dose for each medication. For example, a patient taking a 40 mg daily dose of a drug for which 200 mg was the 'maximum daily dose' was considered to be taking 0.2 'intensity' units. The sum of the proportional doses from individual medications determined a patient's 'treatment intensity score'. By referring the total intensity of treatment to BP control, it became apparent that efficacy of treatment was significantly lower in older hypertensives than in younger hypertensive subjects [24].

Overall, management of high BP in the elderly, in particular in old patients with comorbidities is difficult. Many would agree with Krakoff's statement that 'Older patients need better guidelines for optimal treatment of high blood pressure. One size fits few' [21]. Clinical trials which are currently in progress promise to supply the evidence for optimizing treatment of old hypertensive patients: to identify the most favorable antihypertensive agents for old age groups and the degree to which BP should be lowered for prevention of stroke and cognitive decline [9].

II. BP Control May Be Compromised During Intercurrent Illness

Guidelines for treatment of arterial hypertension assert that after target BP has been achieved, follow-up visits can be limited to every 3 to 6 months; this recommendation is suitable except coexistent conditions require more frequent BP assessment or unless intercurrent illness intervenes [20]. An intercurrent condition, may it be an infection, acute coronary event, stroke, trauma or surgery, possibly will interfere with BP homeostasis; therefore, re-evaluation of the antihypertensive treatment is needed.

Case 1 – Transient Orthostatic Hypotension During Febrile Illness

An 84-year-old woman was admitted to the medical ward for headache, vomiting and refractory hypertension. The patient's history was notable for diabetes mellitus and arterial hypertension diagnosed ten years ago. Lately, the BP was poorly controlled while the patient was taking 3 anti-hypertensive medications. She also suffered form severe anxiety but refused specific treatment. Her medications included clonidine 0.150 mg x 3, amlodipine 10 mg, doxazocin 8 mg and hydrochlothiazide 12.5 mg per day. Physical examination on admission revealed an uncomfortable-looking woman with normal body temperature. Supine BP was 260/123 mmHg. Ophthalmoscopy displayed diffuse arteriolar narrowing and arteriovenous nicking. Laboratory studies were unremarkable except for microalbuminuria; levels of serum creatinine, thyrotrophin and a 24-hour urine collection for catecholamines and urinary free cortisol were within the normal range. The electrocardiogram showed left ventricular hypertrophy. Chest radiography was normal. After addition of lorazepam, the patient felt better. A bedside postural test showed supine BP 190/90 mmHg and standing BP 180/94 mmHg. Computerized tomography (CT) of the brain revealed a small meningioma in the falx. Capoten-enhanced nephrogram was unremarkable. CT-angiography exhibited bulky calcification at the ostium of the left renal artery, and normal diameter and appearance of the renal arteries. Carotid duplex study showed no significant stenosis. The patient did not accept psychiatric consultation. Aldospirone 25 mg was added to the previous drug regimen.

One moth later she was referred to the emergency service because of repeated falls associated with loss of consciousness. The patient's supine BP was 200/97 mmHg, the temperature 39^0C. In suspecting sepsis, the patient was hospitalized and antibiotic treatment was started. Subsequently, E. coli urinary tract infection was diagnosed. The other day syncope was witnessed when the patient aroused from bed. On bed-side postural test, the supine BP was 190/102 mmHg followed after 2 minutes of standing by BP drop to 90/48 mmHg. Accordingly, the anti-hypertensive medications were tapered. One week later the patient had recovered from sepsis; the seated BP at this point in time was in the range 123-164/71-80 mmHg. The patient was discharged with the advice to closely observe the BP at home, both in the sitting and supine positions, and remain under close medical supervision.

This case illustrates the effects of sepsis on the BP. This old woman suffered from severe hypertension, both in the supine and standing positions. Acceptable BP control could be obtained with a combined regimen of clonidine, amlodipine, doxazocin, hydrochlothiazide and spironolactone. However, the hardly achieved BP control was altered when sepsis intervened; at this time the patient developed severe orthostatic hypotension. Thus, the former hypertension pattern characterized by high BP both in supine and erect positions was transiently changed into a pattern of supine hypertension associated with orthostatic hypotension. This effect could be attributed to sepsis for several reasons: there was close temporal coincidence between the occurrence of orthostatic hypotension and occurrence of sepsis and the remission of orthostatic hypotension and the remission of sepsis; no other etiologies of orthostatic hypotension became apparent; the patient's antihypertensive regimen was unchanged at the time orthostatic hypotension occurred; consistency of this observation with similar reports in the literature; biologic plausibility of the causal determinism of orthostatic hypotension by sepsis [25,26].

Preservation of BP depends on factors which affect the cardiac output and the peripheral vascular resistance, according to the equation: BP = cardiac output x peripheral arterial resistance. A decrease in cardiac output or decline of the peripheral arterial resistance, or both will produce a decrease in BP [22]. Circulatory compromise during sepsis is attributed to cytokine-induced vasodilatation, capillary leak, and reduced myocardial contractility [27-30]. Myocardial injury in sepsis occurs more often in severely ill, older patients with underlying cardiovascular disease [31,32]. Cardiac troponin I was increased in 85% of patients with sepsis, septic shock or systemic inflammatory response syndrome [33]. The mechanism by which infection causes cardiac troponin release is not understood. One of the manifestations of circulatory compromise in sepsis is decreased BP [33]. Impaired BP homeostasis in sepsis differs from acute dysautonomia, which may complicate viral infections and may also cause orthostatic hypotension [34,35].

Orthostatic hypotension may be an early sign of sepsis, similar to orthostatic hypotension sometimes being the presenting sign of gastrointestinal bleeding [36]. Though familiar to practitioners, the occurrence of orthostatic hypotension as a presenting feature of sepsis has not been systematically studied (we could not find a quotation on searching the Medline data base).

Learning points:

- BP control may be compromised in sepsis.
- There may be an increased hypotensive effect to usual doses of antihypertensive medications when sepsis intervenes.
- The additive effects on BP of sepsis and antihypertensive medications may cause orthostatic hypotension.
- Orthostatic hypotension occurring with sepsis is transient.

III. Hypertensive Spells

Episodic symptoms including palpitations, pallor, tremor, headache, hypertension, followed by diaphoresis toward the end of the spell are suggestive of pheochromocytoma. However, this syndrome is not specific since patients suspected to have a pheochromocytoma have rarely the diagnosis confirmed [37].

Case 2 – Postural Hypertension

An 87-year-old man was referred to our institution with a 2 months history of hypertensive spells occurring in a stereotypical fashion. As described by caregivers in the nursing home where he was residing, the symptoms occurred 30 to 120 minutes after being seated in a geriatric chair, featuring pallor, muscle rigidity more prominent than usual, increase of the heart rate up to 110 bpm, BP surge up to 210/130 mmHg, profuse sweats, and apparently interruption of urine output (the patient had a permanent urinary catheter). The event was terminated soon when the patient was brought back to bed, with the BP returning

to usual levels of 130/70 mmHg and the subsequent appearance of polyuria (500 cc within an hour). The blood sugar measured at the height of a spell was 118 mg/dL and the body temperature remained normal. There was no link between spells and meals. The patient's medical history was notable for stroke and ensuing vascular dementia 7 years ago, parkinsonism, and the finding of enlarged and hard prostate with high levels of prostate specific antigen (42 ng/mL, normal < 4 ng/mL). Further investigation of suspected prostatic carcinoma was declined by the patient's spouse. The patient's medications were memantine 10 mg twice per day and doxazocin 4 mg/day. Doxazocin has been discontinued and oxycontin was administered for a few days; neither influenced the occurrence of spells.

On physical examination, the patient's temperature was 36.7°C, the heart rate 62 beats/min, BP 130/60 mm Hg, respiratory rate of 18/min, and oxygen saturation 94% while breathing room air. Findings on examination of the lungs, abdomen, and skin were normal. On digital examination the prostate was enlarged and felt hard. Laboratory studies showed normal blood count, liver-function tests, erythrocyte sedimentation rate, lactic dehydrogenase, uric acid, calcium and thyrotrophin.

Orthostatic tests were performed with the aim to reproduce the hypertensive spell and symptoms described by the patient's health care providers. For this purpose a variant of a passive postural test was performed adapted to the patient's special physical condition. A geriatric chair was shifted in supine position with the patient lying on his back for 15 minutes, than the configuration of the chair was changed to sitting for 10 minutes. The BP and heart rate were monitored. Te supine BP was about 130/70 mmHg and the heart rate 73 bpm with minimal variation. The sitting BP progressively increased to 160/76 while the heart rate decreased to 64 bpm. During both phases of the postural test, the oral temperature was 36.4°C and the ECG showed sinus rhythm. The patient's typical spell was not reproduced during the test. These data were interpreted as orthostatic hypertension with adequate baroreflex response of the heart rate. On a different occasion the test was repeated, than the patient was given his regular meal, followed by postprandial BP measurements taken at 10 minute intervals for 2 hours. The results were essentially similar with those recorded on the short orthostatic test. A 24-hour urine collection for catecholamines showed normal epinephrine, norepinephrine, dopamine and metanephrine levels; the collection included a period of continuous sitting in a chair of four hours. In summarizing these findings, the diagnosis of orthostatic hypertension was set.

Orthostatic hypertension is defined as a rise in systolic BP upon assuming upright posture. There is no widely agreed definition of orthostatic hypertension [38] and the diagnostic criteria adopted by different study groups vary: increase in the systolic BP upon assuming upright posture by ≥10 mmHg [39-41] or by ≥5 mmHg in other studies [42]. The prevalence of orthostatic hypertension and its association with morbidity and subsequent mortality was examined prospectively in 3741 Japanese-American men aged 71-93 years. The prevalence of postural hypertension in this cohort was 39%; there were no significant correlations with morbidity and subsequent mortality [41]. The underlying mechanism is thought to involve activation of the sympathetic nervous system, heightened adrenergic reactivity to orthostatic stress associated with an accentuated increase in vascular resistance and BP. Some of the more severely affected patients have baroreflex failure, mastocytosis, hyperadrenergic postural tachycardia syndrome or pheochromocytoma [42]. Postural change,

as in the present case, may also trigger hypertensive spells in patients with pheochromocytoma [43].

Symptoms of pheochromocytomas are caused by tumoral hypersecretion of norepinephrine and epinephrine [43]. The classic triad of symptoms is episodic headache, sweating, and tachycardia. Peripheral vasoconstriction during spells results in cold hands and feet and facial pallor. Sweating is common toward the end of the spell. Paroxysms tend to be stereotypical for each patient, although the symptoms may differ from one patient to the other. Spells may be either spontaneous or precipitated. Precipitating factors are postural change, anxiety, medications (for example anesthetic agents), maneuvers that increase intraabdominal pressure (for example change in position, lifting). The typical duration of a pheochromocytoma spell is 15 to 20 minutes, but it may be much shorter or longer, up to several hours. Spells may occur multiple times daily or infrequently [37,43]. Nearly all patients have increased urinary excretion of catecholamine metabolites (vanilmandelic acid and metanephrines) and free catecholamines. Total metanephrines excretion/24h is the most useful test, but false-positive results may rarely occur [44]. Computerized tomography and MRI are sensitive for the diagnosis of pheochromocytomas (98 to 100%) because most tumors are 3 cm in diameter or larger at the time of clinical presentation; the specificity of CT and MRI for the diagnosis of pheochromocytomas is only 70% because of the high prevalence of adrenal 'incidentalomas.'

Adrenergic spells of various causes, other than pheochromocytoma, are well known. Adrenergic spells may occur in essential HT, baroreflex failure, familial dysautonomia, induced by crack cocaine ingestion, serotonin syndrome, neuroloptic malignant syndrome, spinal cord injury, amyotrophic lateral sclerosis, thyrotoxicosis, insulinoma, diencephalic epilepsy, panic attacks, treatment with monoamine oxidase inhibitor with concomitant ingestion of tyramine or a nasal decongestionant, sympathomimetic ingestion, withdrawal of clonidine, cerebral infarction, and autonomic epilepsy [37,45-51].

In our patient, the main diagnostic considerations were adverse effects of medications (but he was receiving only memantine which has not been shown to cause adrenergic hyperactivity) [52], pheochromocytoma (but urinary catecholamines were in the normal range) and an obscure neurological cause. Eventually, the tentative diagnosis of idiopathic postural hypertension was suggested. A therapeutic trial with tamsulosine 5 mg/day, which may be useful in the treatment of sympathetic hyperactivity [51], was of no avail.

Learning points:

- Orthostatic hypertension is defined as a rise in systolic BP upon assuming upright posture by ≥10 mmHg**.**
- Orthostatic hypertension is common in elderly persons and most often no underlying cause can be found.
- Orthostatic hypertension may occasionally be a manifestation of pheochromocytoma since postural change may trigger an adrenergic crisis**.**
- Adrenergic spells similar to those of pheochromocytoma may occur in a variety of disorders.
- Among patients suspected to have pheochromocytoma the diagnosis is rarely confirmed and other causes should be looked for.

IV. Standards of BP Measurement in Acute Geriatric Care

The mercury sphygmomanometer has been regarded as the gold standard for clinical measurement of BP. The readings are based on Korotkoff's sound technique, and are taken by a trained health care provider [53]. Yet, even by using the gold standard procedure, misclassifications in BP diagnosis may occur for several reasons. First, inaccuracies exist of indirect BP measurement as compared to intra-arterial BP measurement. The Korotkoff technique tends to give values for systolic pressure that are lower than the true intra-arterial pressure, and diastolic values that are higher [54,55]. In older patients with a wide pulse pressure, the Korotkoff sounds may become inaudible between the systolic and diastolic pressure, and reappear as the cuff deflation is continued. This phenomenon is known as the auscultatory gap. The auscultatory gap often can be eliminated by elevating the patient's arm overhead for 30 seconds before inflating the cuff and then bringing the arm to the usual position to continue the measurement. This BP measurement gap is not a problem with non-auscultatory methods. Second, day-to-day variabilities of the BP and seasonal variabilities exist, so one day's measurement may not be representative to the patient's usual BP. Third, situations labeled as 'white-coat hypertension', 'masked hypertension' and 'pseudohypertension' may cause misclassification of BP diagnosis. Actually, in 15% to 20% of people with stage 1 hypertension the BP may be elevated only in the presence of a nurse of physician. When measured elsewhere, including at work, the BP is not elevated. When this phenomenon is detected in patients not taking medications, it is referred to as 'white-coat hypertension'. White-coat hypertension is more common in older persons. 'Masked hypertension' is the converse condition, characterized by normal BP in the office and elevated BP at work or at home. Lifestyle can contribute to occurrence of masked hypertension, as well as alcohol, tobacco, caffeine consumption, and physical activity away from the clinic. 'Pseudohypertension' is caused by rigidity of the peripheral arteries because of advanced arteriosclerosis, when the cuff has to be inflated at a higher pressure to compress the brachial artery. Osler's maneuver can be used to confirm a suspicion of pseudohypertension. This consists of assessing the palpability of the radial artery after making it pulseless by compressing the homolateral brachial artery with cuff pressure. If so compressed, the normal radial artery is not identifiable by palpation; in contradistinction, a stiffened artery may be palpable and if so is labeled Osler-positive [56]. Osler's sign was present in 7.2% of persons older than 59 years screened for the Systolic Hypertension in the Elderly Program study [57]. However, Osler's maneuver is not a reliable test of pseudohypertension; in a study 57% of Osler-positive elderly patients were found to be normotensive by intra-arterial BP measurement [58]. Erroneous BP diagnosis because of white-coat hypertension or pseudohypertension may result in the patients' over treatment with antihypertensive medications and ensuing adverse effects, including orthostatic hypotension.

Aneroid sphygmomanometers register the pressure with the aid of a mechanical system of metal bellows that expand as the cuff pressure increases. The readings are based on Korotkoff's sound technique with the inherent shortages. This system does not necessarily maintain its stability over time, and therefore calibrations are required at regular intervals.

Automated oscillometric BP devices are increasingly used. Oscillometric BP monitors detect motion of the BP cuff transmitted from the underlying artery. A sudden increase in the amplitude of arterial oscillations occurs at systolic pressure and mean arterial pressure, and an abrupt decrease occurs at diastolic pressure. One advantage of the method is that the transducer needs not to be placed exactly over the brachial artery, so that placement of the cuff is not critical. Other potential advantages of the oscillometric method are that it is less susceptible to external noise (but not to low-frequency mechanical vibration). The main problem with this technique is that the amplitude of the oscillations additionally depends on factors other than BP, most importantly the stiffness of the arteries. Oscillometric BP measurements may be *patient dependent,* hence, the disagreement between oscillometric BP measurements and mercury sphygmomanometry may vary from patient to patient [59]. In older people with stiff arteries and wide pulse pressures the mean arterial pressure may be significantly underestimated by oscillometric BP measurements [60]. Oscillometric BP measurements are *device dependent,* because the algorithms used to detect the systolic and diastolic BP differ from one device to the other. This has been illustrated by using simulated pressure waves: for a systolic pressure of 120 mm Hg different devices measured pressures as low as 110 mmHg and as high as 125 mm Hg [61]. *Inconsistence* of measurements by the same device and in the same patient may exist. Furthermore, the disagreement between oscillometric and sphygmomanometric measurements may largely fluctuate on sequential measurements in the same patient [62,63]. Therefore, the demand remains for more accurate and stable automatic BP measurement devices.

The Duo Sensor technology is one such development [64], customized to combine the comfort of the oscillometric measurement with the accuracy of the Korotkoff-method. It is also suitable for patients with arrhythmias, conditions known to flaw readings by common oscillometric devices. The Tensoval device that is based on the duo sensor technology has been validated according to the criteria of the BHS protocol and the International Protocol and qualified A/A grade [64]; this device has been recommended for clinical and home care use.

Other automatic BP measurement devices incorporate an ultrasound receiver and transmitter placed over the brachial artery under a sphygmomanometer cuff. As the cuff pressure falls below the brachial artery pressure the artery opens. The opening movement produces a Doppler shift which corresponds to the first Korotkoff sound. Instruments based on this method may provide reliable BP measurements in severe hypotensive states and unfavorable conditions when other indirect BP measurement methods usually fail [65].

Beat-to-beat BP monitoring based on the finger cuff method of Penaz detects arterial pulsations in a finger by a photoplethysmograph under a pressure cuff. The output of the plethysmograph is used to drive a servo-loop, which rapidly changes the cuff pressure to keep the output constant, so that the artery is held in a partially opened state. The oscillations of pressure in the cuff are measured and have been found to resemble the intra-arterial pressure wave in most subjects. It is commercially available as the Finometer (formerly Finapres) and Portapres recorders, and has been validated in several studies against intra-arterial pressures [66,67]. Its greatest value is for research, assessing short-term changes of BP and its variability. Beat-to-beat BP monitoring is also possible by tonometry; the latter is based on the principle that an artery partially compressed or splinted against a bone exhibits pulsations

that are proportional to the intra-arterial pressure. By this method, the BP is recorded at the wrist, where the radial artery lies just over the radius bone [68]. For tonometry, the transducer needs to be situated directly over the center of the artery. Hence, the signal is very position-sensitive, requires calibration in each patient and is not suitable for routine clinical use.

The central arterial BP may be assessed indirectly by applanation tonometry. Current computer software allows calculation of the central aortic pressure and waveform from the radial pulse pressure waveform, using peripheral BP measured at the brachial artery. The BP waves differ markedly between central and peripheral sites of the arterial bed. Therefore the question is whether evaluation of central BP by indirect methods may give additional data for the stratification of cardiovascular risk and for the management of arterial hypertension. Unfortunately, the accuracy of estimated central BP is suboptimal as shown by comparisons with directly recorded aortic pressure during cardiac catheterization. So the technique cannot be recommended for standard clinical practice [69-71].

In the acute care setting, BP measurements are routinely performed with oscillometric devices because the simplicity of their use. The 'gold standard' device for office BP measurement has been the mercury sphygmomanometer, but these instruments are being removed from practice because of environmental concerns about mercury contamination [72]. Mercury sphygmomanometers are the standard of reference when measurements obtained with an automatic device are suspicious.

Also, mercury sphygmomanometers are essential for evaluating the accuracy of any type of non-mercury devices [53].

Accuracy of Devices

Automated BP measurement devices should be subjected to formal validation protocols. The two protocols that gained the widest acceptance were developed by the Association for the Advancement of Medical Instrumentation (AAMI) in 1987 and by the British Hypertension Society (BHS) in 1990, with revisions to both in 1993, and to AAMI in 2002 [73]. These protocols require testing of a device against mercury sphygmomanometry performed by two trained human observers in 85 subjects. Thus validation studies are difficult to perform. One consequence is that there are still many devices on the market that have not been adequately validated. Manufacturers are not obliged to guarantee the accuracy of their product, although most reputable manufacturers have their devices evaluated independently according to a generally accepted protocol. More recently, an international group of experts has proposed a validation protocol, named the International Protocol, that is easy to perform and could replace the 2 earlier versions [74]. The validation procedure is confined to adults over the age of 30 years and does not make recommendations for special groups, such as children, pregnant women and the elderly, or for special circumstances, for example exercise. It is anticipated that the relative ease of performance of the International Protocol will encourage manufacturers to submit blood pressure measuring devices for validation in order to obtain the minimum approval necessary for a device to be used in clinical medicine, and that, in time, most devices on the market will be assessed according to the protocol for basic accuracy. It does not preclude

manufacturers of devices from subjecting their products to more rigorous assessment and validation.

The fact that a device passed a validation test does not mean that it will provide accurate readings in all patients. There can be substantial numbers of persons in whom the error is consistently >5 mm Hg with a device that has achieved a passing grade [75]. This may be more likely to occur in elderly patients [76].

The accuracy of mercury and aneroid monitors also needs to be checked. In the case of mercury sphygmomanometers, this involves checking that the upper curve of the meniscus of the mercury column is at 0 mm Hg, that the column is free of dirt, and that it rises and falls freely during cuff inflation and deflation. Aneroid devices or other non-mercury devices should be checked by connecting the manometer to a mercury column or an electronic testing device with a Y-tube [53].

Learning points:

- Though the mercury sphygmomanometer is the 'gold standard' device for indirect BP measurement, its use has been restricted in clinical practice because of concerns about mercury contamination.
- Instead, automated oscillometric BP devices have get preponderance mainly for their versatility.
- Accuracy of oscillometric BP measurements may vary. The fact that a device passed a validation test does not mean that it will provide accurate readings in all patients.
- Oscillometric BP measurements may be patient dependent**.**
- The difference between oscillometric and sphygmomanometric measurements may be clinically important.
- Therefore, the patients' BP should be measured both with the mercury sphygmomanometer and an automatic oscillometric device. If there is agreement between readings measurements can be taken confidently with the oscillometric device.

V. Frequency of BP Measurements in Acute Geriatric Care

There is no agreed answer to the questions how often, at what time of the day, and in which position should the BP be measured in patients hospitalized in the geriatric ward. Our routine is based on the following principles (Figures 1 and 2):

1. On admission to the ward, BP measurements are performed with a mercury column sphygmomanometer (Baumanometer, standby model 0661-0250) by a trained nurse. Measurements are performed on both arms; the arm with the higher BP is chosen for ensuing measurements. Oscillometric BP measurements follow. If there is agreement between readings obtained with the manual and automatic instrument for systolic and diastolic BP within 5 mm Hg of each other, subsequent measurements are taken with the oscillometric device.

2. The Datascope Accutor Plus automatic oscillometer is utilized in our ward, a device that qualified A/A on the British Hypertension Society validation protocol. The frequency of measurements is set in conformity with the patients' general condition and hemodynamic stability.
3. In the emergency setting, such as pulmonary edema, acute coronary event, severe hypertension, severe hypotension or shock, the BP is measured automatically in the 'continuous mode' at 2 to 5 minute intervals, until the patient is transferred to the intensive care unit.
4. Patients with sepsis, dehydration, severe heart failure or tachypnea have supine BP measured three times per day. More frequent measurements are taken in instances of hemodynamic instability.
5. Patients complaining of falls, syncope or dizziness undergo a bedside orthostatic test, at least once, as well as postprandial BP monitoring in the seated position (see details in the chapter ' Syncope in the elderly - focus on orthostatic hypotension').
6. Patients recovering from an acute illness (sepsis, diarrhea, intensive diuresis) undergo a bedside orthostatic test before ambulation.
7. Hypertensive patients have BP measurements taken three times per day in the sitting position and once have a bedside orthostatic test performed.
8. Patients with supine hypertension and associated orthostatic hypotension require a more comprehensive work-up: orthostatic tests are performed at baseline; follow-up orthostatic tests to observe the effects of treatment; postprandial BP monitoring in the seated position; one hour after a meal the patients is asked to walk for five minutes then immediately the standing BP is measured; supine BP measurements during sleep (see chapter 'Syncope in the elderly - focus on orthostatic hypotension').
9. Hemodynamically stable patients with no acute illness are measured the BP once daily in the seated position.
10. Unexpected BP values, contrasting with the patient's usual BP, require immediate confirmation, double check with the mercury sphygmomanometer, as well as search for undue medications, intercurrent illness or exogenous influences.

In conclusion, arterial hypertension or hypotension are common in elderly patients. BP homeostasis may be further impaired by an intercurrent illness. Hypotensive syndromes as well as uncontrolled hypertension represent common problems in patients admitted to the acute geriatric ward. Competence in this field is mandatory.

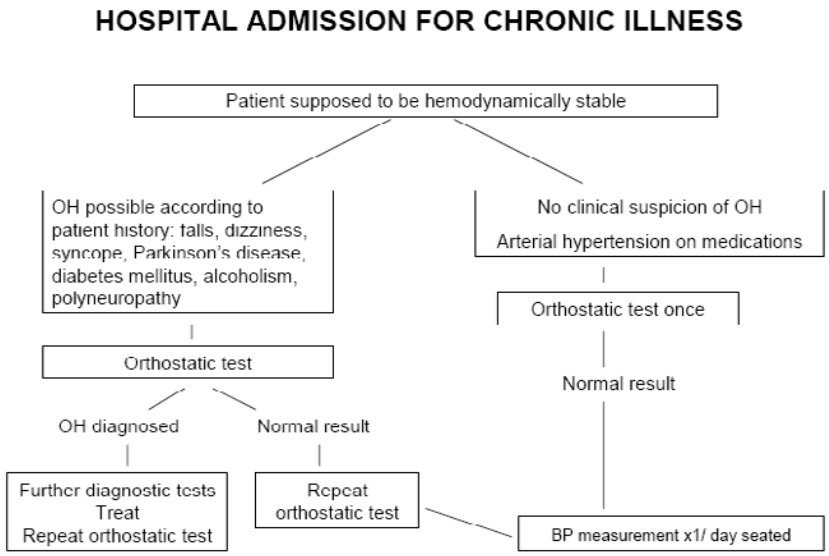

Figure 1. Protocol of BP measurements for hemodynamically stable patients admitted to the geriatric ward.

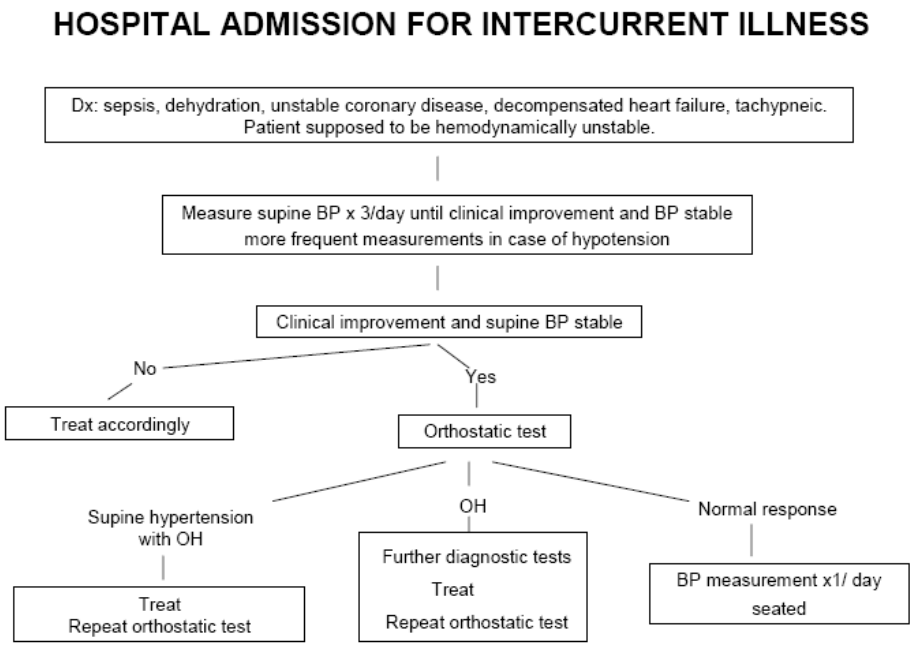

Figure 2. Protocol of BP measurements for hemodynamically unstable patients admitted to the geriatric ward.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter II

Syncope in the Elderly - Focus on Orthostatic Hypotension

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Syncope is defined as a sudden and brief loss of consciousness and postural tone from which recovery is spontaneous and the underlying mechanism is transient global cerebral hypoperfusion [1]. Cerebral hypoperfusion may result from different disturbances: decreased cardiac output (cardiac syncope), vasodilatation, hypovolemia, increased cerebral vascular resistance, or cerebral steel. Consciousness is lost when the cerebral blood flow ceases for 6 to 8 seconds, or the mean arterial blood pressure (BP) drops to ≤60 mmHg, or cerebral oxygen supply decreases below 3.5 ml O_2/100 g brain tissue/min [1]. A syncopal episode can lead to injury, fear, and functional limitation. Proper management is essential to maintain maximum patient independence [2].

I. Syncope in the Elderly

Syncope accounts for approximately 3% of emergency department visits and 1% to 6% of medical admissions to a general hospital. Syncope is a common problem in elderly persons. The prevalent causes of syncope in elderly patients differ from those in younger individuals. So, cardiac diseases, orthostatic hypotension (OH) and postprandial hypotension are frequent causes of syncope in the elderly, carotid sinus hypersensitivity is more common in the elderly than in young, while vasovagal syncope is more common in young persons and goes often undiagnosed in the elderly [3-6]. OH, whether it occurs after administration of medications, standing up, or after a meal is an important and often reversible disorder in older persons.

This article brings in focus OH in elderly patients, a condition not as easily diagnosed and more difficult to treat as it would appear.

II. Orthostatic Hypotension

Orthostatic hypotension has been formally defined by expert consensus as a fall in systolic BP of at least 20 mmHg and or diastolic blood BP of at least 10 mmHg within 3 minutes of standing [7]. When a normal individual stands, 10% to 15% of the blood is pooled in the legs thereby secondarily reducing venous return, cardiac output and arterial pressure. This fall in BP activates arterial baroreceptors with a subsequent reflex increase in sympathetic outflow and parasympathetic inhibition, leading in turn to peripheral vasoconstriction and increased heart rate and contractility. There may be a slight fall in systolic BP, a slight rise in diastolic BP and a mild increase in heart rate accompanying this chain of events [8]. OH is an excessive fall in BP occurring early on orthostatic challenge when orthostatic stress overwhelms autonomic defenses [9]. Numerous factors may influence BP homeostasis and impact on the occurrence of OH: autonomic nervous system function, intravascular volume, duration of erect posture, time of the day, postprandial state and ambient temperature [10,11]. The most common causes of OH in the elderly are side effects of medications, in particular diuretics, nitrates, antihypertensive and tricyclic antidepressant drugs. Autonomic neuropathies, whether primary (primary autonomic failure, multiple system atrophy and Parkinson's disease) or secondary (diabetic, chronic renal failure, chronic liver disease, alcohol-induced, Vit B12 deficiency, Guillain-Barre syndrome, paraneoplastic, etc) frequently manifest with OH. Symptoms of OH often begin within seconds of standing up and oblige the patient to lie down to prevent syncope; the diagnosis is obvious [7,12,13]. So, dizziness and syncope when getting up are typical symptoms of OH. However, the relationship of other symptoms to OH may not be apparent unless one is aware of the wider spectrum of orthostatic disturbances. Thus, weakness, fatigue, visual blurring, vertigo, suboccipital and paracervical pain, chest pain on upright posture, headaches, palpitations, low back pain or dyspnea may occur on standing and disappear when lying flat, being the predominant symptoms of OH in a number of patients [14-16].

The diagnostic consensus criteria defining OH [7] are necessarily arbitrary. There are questions open as to the magnitude of hypotension and rapidity of its development in the definition of OH. Patients may feel dizzy, weak or even faint upon standing while orthostatic BP decrement is insufficient to meet the criteria for OH [17-19]; one may still consider OH as a possible diagnosis in these patients [14]. In limiting one's self to the consensus criteria for the definition of OH [7] one may lose useful clinical information [20]. Basically, OH is a physical finding and not a diagnosis; OH evaluation and therapy are primarily driven by symptoms [21].

Aging is associated with increased risk of OH In community dwelling individuals more than 65 years of age, the prevalence of OH is approximately 20%; in those older than 75 years the prevalence is as high as 30%. In frail elderly individuals living in nursing homes, the prevalence of OH may be as high us 50% [22]. The prevalence of OH among patients presenting with syncope in the emergency room was 24% in one study [23] and 64% among elderly patients hospitalized for acute conditions [24].

The increased prevalence of OH in the elderly may be explained by age-associated alterations that affect BP regulation [3,25,26]: decreased baroreceptor sensitivity, decreased alfa-1-adrenergic response to sympathetic stimulation, decreased renal sodium conservation,

increased vascular stiffness, reduced left ventricular diastolic filling, increased venous system tortuosity. The heart rate response to hypotensive maneuvers, exercise or isoproterenol infusion is decreased. The levels of renin, angiotensin, aldosterone and arginine-vasopressin are lower in elderly persons and also have blunted responses to upright posture. Natriuretic peptide levels increase with age, and the hypotensive response to natriuretic peptide infusion is enhanced in the old. Volume depletion causes greater orthostatic BP declines in the old than in younger subjects. Postprandial BP declines occur frequently in elderly subjects but not in the young [27]. Moreover, for any decrease in BP elderly persons are also more likely to become symptomatic because of the high likelihood of cerebro-vascular disease and the rightward shift in cerebral autoregulation which occurs with hypertension.

Importance of diagnosing OH is manifold: OH may underlie symptoms of cerebral hypoperfusion, OH is marker of frailness, a risk factor for falls [28], a predictor of ischemic stroke [29], cardiovascular mortality and all-cause mortality [30,31].

OH Variants

OH may be classified according to etiology, time of onset on orthostatic challenge, the pattern of BP change, and the chief hemodynamic mechanisms involved (Table 1). The etiology of OH includes three main categories: autonomic failure, hypovolemia, and adverse effect of vasodilators.

Table 1. OH classification

1. Etiology
- autonomic failure
- hypovolemia
- vasodilators
2. Time of onset
- early OH (between min 1-3 of orthostatic challenge)
- delayed OH (between 5 min and 45 min of orthostatic challenge)
- initial OH (within 15 s after standing up)
3. Pattern of BP drop
- transient
- stable
- progressive
4. Hemodynamics
- arteriolar dysfunction
- venular dysfunction
- mixed

In considering *the time to onset of OH* on orthostatic challenge, three categories have been described: 'early OH', that is the common variant with onset between 1 min and 3 minutes of orthostatic challenge; 'initial OH' developing within 15 seconds after standing up; 'delayed OH' with onset between 5 min and 45 min of orthostatic challenge [27]. Streeten et al. first drew attention to 'delayed OH', which occurred after 13 to 30 minutes of standing [32]. Freeman et al. reviewed the records and autonomic test results of patients referred for evaluation of dysautonomia; they noticed that delayed OH occurred as frequently as early OH: out of 108 patients having OH on tilt test, 46% developed OH in the first 3 minutes of head-up tilt, 3% between 3 and 5 minutes, 12% between 5 and 10 minutes and 39% after 10 minutes of tilt [33]. The recently described 'initial OH' is quite different from other variants of OH: it is triggered by standing but not by passive orthostatic maneuvers, neither by sitting up or by head-up tilt; it manifests within 15 seconds of standing; the magnitude of the systolic BP drop by definition of 'initial OH' is ≥40 mmHg and/or diastolic BP drop ≥20 mmHg; the event is associated with symptoms of cerebral hypoperfusion [34]. The pathophysiological mechanism involved in 'initial OH' is thought to be a temporal mismatch between cardiac output and vascular resistance. The diagnosis of 'initial OH' can be established only by beat-to-beat BP recording during active standing-up. Few treatment options are available. Lower body muscle tensing may attenuate the transient BP decrease after standing up, and the patients may benefit from this maneuver [35].

Patterns of OH illustrate the time course of the systolic BP during the initial five minutes of tilt [36]. The following patterns are recognized: stable systolic OH, transient systolic OH with either early or late partial recovery, and progressive systolic OH with continuous decrease in BP. Patients with progressive OH have significantly higher scores on the adrenergic subscale of the Composite Autonomic Symptom Score and are assumed to have more severe adrenergic impairment. The progressive systolic OH pattern predicts increased risk of developing syncope on continuing orthostatic challenge [36,37].

The prevailing hemodynamic disturbance in OH is another principle for OH classification. Non-invasive beat-to-beat recording of the BP and heart rate, computing the total peripheral resistance (TPR) and cardiac output (CO) during orthostatic challenge is possible with the aid of the Finometer. Based on changes in TPR and CO during orthostatic challenge, three categories of OH were described [38]. First, OH characterized by arteriolar dysfunction is recognized by a drop in TPR during head-up tilt leading to a drop in BP despite an increase in CO. Second, OH caused by venular dysfunction is characterized by reduction in CO leading to a drop in BP despite compensatory increase in TPR. Third, mixed dysfunction that is characterized by the simultaneous occurrence of arteriolar and venular dysfunction. It was suggested that therapeutic interventions might be specifically directed at the hemodynamic mechanism involved in OH. Thus, midodrine, an alpha-1 agonist which causes arteriolar and venous vasoconstriction, would be an appropriate choice in the treatment of arteriolar OH. For venular OH, pressure stockings or fludrocortisone would be the preferred options [38].

Orthostatic Stress Tests

The diagnosis of OH is influenced by the BP measurement technique, the positioning of the patient and timing of the measurements [39]. A detailed review on this topic has been presented in a recent review article [20]. Three orthostatic tests are widely applied in practice: the lying-to-standing test, lying-to-sitting test and the head-up tilt test. Few studies have compared results of different orthostatic tests directly [40,41]. Lower body negative pressure tests are mainly used in research settings [42].

The lying-to-standing orthostatic test A frequently utilized protocol is the short, bedside orthostatic test. According to a commonly used protocol, the patient's BP and heart rate are recorded after 5 to 10 minutes of rest in the supine position. Next, the patient arises and the measurements are repeated while he stands motionless for 3 to 5 minutes with the cuffed arm supported at heart level. Along the test the patient is asked to report dizziness, faintness or light-headedness, with the examiner recording the transience or persistence of the symptoms. The procedure is aborted for safety reasons if the BP drops precipitously or presyncope ensues. Patients with severe autonomic failure have an immediate drop in BP on standing and OH is easily diagnosed with this simple method [10,39,43]. However, when the onset of hypotension on standing is delayed the diagnosis of OH may be missed on the short bedside orthostatic test [32,41].

The lying-to-sitting orthostatic test has not been standardized [44-48]. One frequently used protocol involves a single BP measurement after prolonged recumbence followed by BP measurements after 1, 3 and 5 minutes of sitting [46]. Other technical details are similar to the supine-to-standing test.

The head-up tilt test allows for a more accurate evaluation of the hemodynamic response to orthostatic challenge. This method utilizes a controlled passive orthostatic stress to challenge the cardiovascular response as measured in BP and heart rate changes. The head-up tilt test comprises a supine pre-tilt phase and the passive head-up tilt. Various protocols are used in performing this test. According to recommendations of the European Society of Cardiology, the supine pre-tilt phase should last at least 5 minutes, when no venous cannulation is performed, and at least 20 minutes when venous blood sampling is part of the study; the tilt angle recommended is 60 to 70 degrees; the duration of passive tilt should be a minimum of 20 minutes and maximum of 45 minutes [43,48]. The BP can be measured conveniently with a mercury column sphygmomanometer or automatic tensiometer at pre-established intervals and the heart rate recorded on an electrocardiographic monitor. Continuous BP and heart rate monitoring with finger plethysmography is preferable to discontinuous measurement [49].

Clear guidelines for the *supine resting time* necessary to achieve stable BP levels are scant. In a study of healthy elderly subjects, a 5 min supine rest ensured reliable and reproducible baseline BP values recorded by Finapres; however, at least 12 min of rest were necessary to obtain full hemodynamic stability in elderly patients with diminished cardiac compliance [50]. In other studies, the recommended time of supine rest before measuring supine BP and starting a orthostatic challenge varied from 5 minutes [31], 5 to 10 minutes [30,43], 15 minutes or more [50], or at 'first morning standing up' [24].

Institutional protocols largely differ. Gupta et al [3] suggested a simple approach to diagnose OH, as follows: First, the BP and heart rate are measured after the patient has been quietly supine for at least 5 minutes and again after 1 minute and 3 minutes of standing. Early morning measurements, especially after a high carbohydrate meal, are useful to identify postprandial hypotension. Detection of OH may require multiple measurements on different days. This can be accomplished with ambulatory BP monitoring, or by lending the patient an automatic BP device with instructions to maintain a diary with recordings of supine and standing BP at different times of the day for several days.

Another frequently used protocol entails a period of supine rest for 15 minutes, with the BP and heart rate recorded every minute during the last five minutes of recumbence. Next, the patient is asked to stand up, or if unable, he is helped to sit up comfortably on the bed's margin with the soles touching the floor. In the standing (or sitting) position, with the cuffed arm supported at heart level, the BP and heart rate are recorded every minute for five minutes, after which the test is terminated. More frequent measurements are taken when the patient reports dizziness or faintness; the test is discontinued in the event of loss of consciousness. This protocol was applied to all patients reported in the following case histories.

Continuous BP and heart rate monitoring with finger plethysmography is preferable to discontinuous measurement [49]. It may enable to diagnose initial OH, identify the chief hemodynamic mechanism involved in OH, differentiate OH from reflex syncope in dubious cases, and diagnose delayed OH by applying longer orthostatic challenges.

Variability of OH

Variability of orthostatic responses is well documented, with diurnal, day-to-day and seasonal patterns. OH was most prevalent and severe in the morning, when subjects first arose and OH may be underestimated when orthostatic testing is performed in the afternoon [51,52]. Observations have suggested the existence of day-to-day variability in BP reactivity to orthostatic stress [51,53]. In one representative study performed in a morning outpatient clinic, 40 elderly persons presenting with orthostatic symptoms of dizziness, falls or syncope were recruited. All patients had a symptomatic drop in orthostatic systolic BP of more than 20 mmHg documented in the clinic. BP and heart rate measurements were repeated on two further morning clinic visits. A total of 67.5% patients had a drop in systolic BP of more than 20 mmHg on both subsequent visits; in the remainder, the initial response was not reproduced. Among those with abnormal autonomic function tests, OH was reproducible in 79%, while among subjects with normal autonomic function tests only 57% had OH reproduced [54]. Seasonal variations in OH have also been noted, OH being more prevalent in summer than in winter [55].

III. Postprandial Hypotension

Analogous to OH, postprandial hypotension is commonly defined in the literature as a decrease in systolic BP of ≥20 mmHg within 2 hours of beginning a meal [56]. The value of this definition is unclear since a BP decrease after a meal to a similar degree is often asymptomatic, and a potential cumulative effect of multiple hypotensive stressors such as sitting and administration of medications at the time of the meal makes it sometimes difficult to attribute postprandial hypotension to the meal.

Postprandial hypotension is distinct from OH: it may occur in the supine position, or when occurring while the patient is sitting after a meal the postprandial hypotension may resolve upon standing up and walking [57]. Often, however, postprandial hypotension occurs concomitantly with OH. In a study of OH and postprandial hypotension among geriatric patients [58], postprandial hypotension was noticed in 67% of the patients, with a significant post-meal systolic BP decrease of 34 +/- 4 mmHg; OH was present in 52% of the patients, with a mean systolic BP decline of 44 +/- 4 mmHg after standing; there was a high statistical probability that OH and postprandial hypotension occur simultaneously.

Because both postprandial hypotension and OH are common in the elderly population, it was proposed that tests for diagnosing hypotensive syndromes should be part of a comprehensive geriatric assessment [56-59]. Automated ambulatory BP monitoring is a simple and inexpensive way in which the diagnosis of postprandial hypotension can be improved [60,61]. But automatic monitoring performs as a nasty witness, not providing the possibility to immediately curb an emerging severe and lasting hypotension.

IV. OH in Acute Geriatric Care

Diagnosis and treatment of OH may be challenging. Strict adherence to guidelines is advisable as illustrated by the following case histories.

Case 1 - venous insufficiency A 72-year-old woman was referred to our hospital with a 3-week history of falls with loss of consciousness, occurring immediately after she was arising from bed. She denied recent fever, diarrhea or vomiting. The patient’s medical history included stable ischemic angina pectoris and hyperlipidemia. The patient has being treated with aspirin 100 mg, simvastatin 20 mg and altenolol 25 mg/day. She did not smoke and did not use alcohol. On physical examination, there were grade 1 ankle edema, abundant reticular veins, protuberant subcutaneous varicosities, engorged calf and saphenous veins with downward-going impulse on coughing. The patient's supine BP was 146/78 mmHg and the pulse rate was 62 bpm. After two minutes of sitting up the BP dropped to 80/62 mmHg and the heart rate increased to 76 bpm, whilst the patient complained of weakness and dizziness. Findings on the remainder of the physical examination and the neurological examination were unremarkable. Results of the routine laboratory tests were within the normal range, the BUN was 18 mg/dL and hemoccult for blood in stool was negative. Electrocardiography showed left ventricular hypertrophy with secondary ST-T changes. Echocardiography showed mild diastolic dysfunction with normal left ventricular systolic function. The patient's severe OH was attributed to venous insufficiency. Elastic bandages were applied to the calves

and thighs. On repeated bedside supine-to-standing orthostatic testing, contrary to expectation, there was no improvement. Again, on the following day, OH was disabling. On examining the bandages it turned out that they were loosely sitting. When the bandages were properly stretched to an estimated 30 mmHg pressure, the orthostatic tolerance improved (Figure 1). Now, the patient was able to sit for several hours.

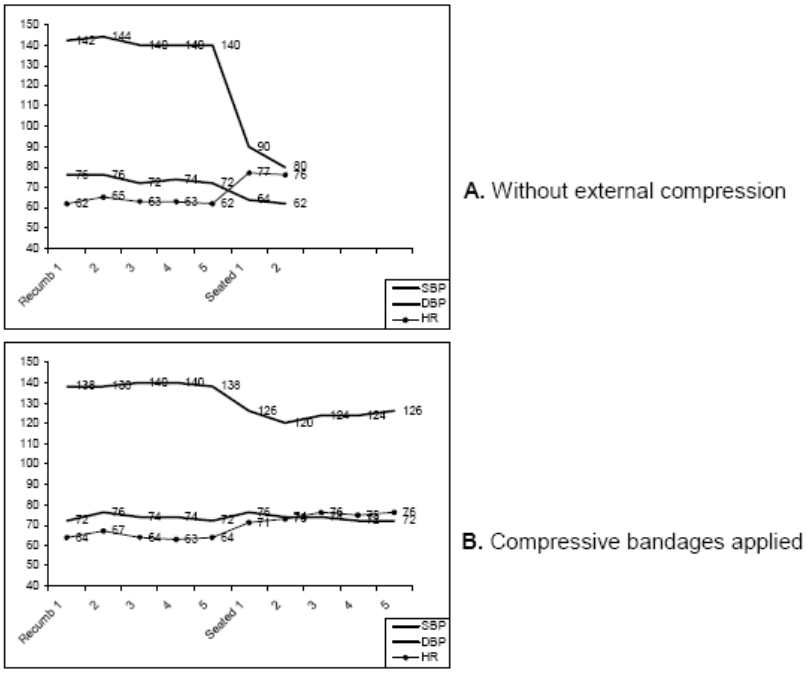

Figure 1. Supine-to-standing orthostatic test in a patient with venous insufficiency and OH. A. Severe OH occurred upon standing. B. Test repeated after application of compression bandages to the calves and thighs: OH prevented.

Although the exact mechanism by which compression is beneficial is not fully understood, a number of physiologic alterations have been observed during elastic compression. These include decrease in ambulatory venous pressure, increase in subcutaneous pressure which counters transcapillary fluid leakage, and improvement in skin microcirculation [62]. Patients are instructed to put on the compression stockings as soon as the day begins, since swelling with standing will make stocking placement difficult, to wear them during the day, and to take them off when going to bed [62-64]. Care must be taken with patients who have concomitant arterial insufficiency because the compression stockings may hinder arterial outflow to the foot [62]. The degree of compression must be modified when mixed venous/arterial disease is confirmed during the diagnostic work-up. The ankle brachial index (ABI) is an important factor to consider in determining compression appropriateness. Compression is contraindicated if ABI <0.5, extreme caution for ABI >0.5 <0.8 [65]. Compression stockings should be used with caution in patients with limited cardiac reserve, because a rapid increase in central blood volume may cause pulmonary edema in the predisposed [66].

Learning points:

- Severe OH may be caused by venous insufficiency.
- Compression treatment correctly applied is highly efficient in such case.

Case 2 – supine hypertension with OH. An 87-year-old man was referred to our institution with a history recurrent falls and severe OH. Dementia with Lewy bodies has been diagnosed 12 month previously, based on insidious onset and progressive cognitive decline, parkinsonism, visual hallucinations, sleep disturbance and repeated falls. Computed tomography showed mild cerebral atrophy. Serum levels of vitamine B12, folate, calcium, sodium, and thyrotrophine were within the normal range. He had no other significant medical history. The patient was being treated with midodrine 5 mg x 2/day, fludrocortisone 0.05 mg/day and aspirin 100 mg/day. The BP was poorly controlled, with supine BP at times as high as 210/98 mmHg and the lowest reported seated BP 80/50 mmHg. At the time of admission, the patient's supine BP was 165/98 mmHg, the pulse was regular at 68/min. After one minute of sitting the BP dropped to 80/44 mmHg with little change during an additional five minutes of sitting. There was resting tremor, muscle rigidity and parkinsonian gait. Results of routine laboratory tests, electrocardiogram and chest X-rays were unremarkable. The most important problem at this point was management of the syndrome of supine hypertension associated with OH. The commonly used treatment regiment for this syndrome was instituted [67]. During day-time, increased fluid intake, low-stretch compression bandages to the calves and thighs, oral midodrine 7.5 mg x 2 and fludrocortisone 0.1 mg x 2/day were prescribed, and emphasis was given to avoid recumbence. Over night, the bandages were removed and a nitroglycerine 10 mg trans-dermal patch was applied (to be removed shortly before standing up). The patient reported to feel better. Orthostatic tests repeated on consecutive days consistently showed seated systolic BP in the range 100 to 120 mmHg and diastolic BP 60 to 80 mmHg. Postprandial BP monitoring for 45 minutes showed systolic BP in the range 126 to 191 mmHg (median 146) and diastolic BP in the range 65 to 86 mmHg (median 78). Supine BP at 11 p.m. was 137/81 mmHg and at 6 a.m. 123/86 mmHg. Unexpectedly, a follow-up orthostatic test showed significant BP drop in the seated position (Figure 2A). The cause was recognized in noticing that the attendant nurse had forgotten to remove the nitroglycerine patch before the patient was standing up that morning. Shortly after the patch was removed and the orthostatic test repeated, the sitting BP met the goal (Figure 2B). As expected, having discontinued transdermal nitroglycerin, the supine BP increased considerably.

This observation carries a double message: first, nitroglycerin is an effective and versatile treatment of supine hypertension [68] and, second, failure to remove the nitroglycerine patch before arising from bed may enhance the OH and carefully should be avoided. The particular variant of OH noticed in this patients is the paradoxical 'hyper-hypo syndrome', that is the association of supine hypertension with OH. This syndrome poses a therapeutic dilemma because treatment of each of the two aspects of the disorder may worsen the other. The approach to the diagnosis and treatment of supine hypertension and associated OH has been well described in the literature [67-69].

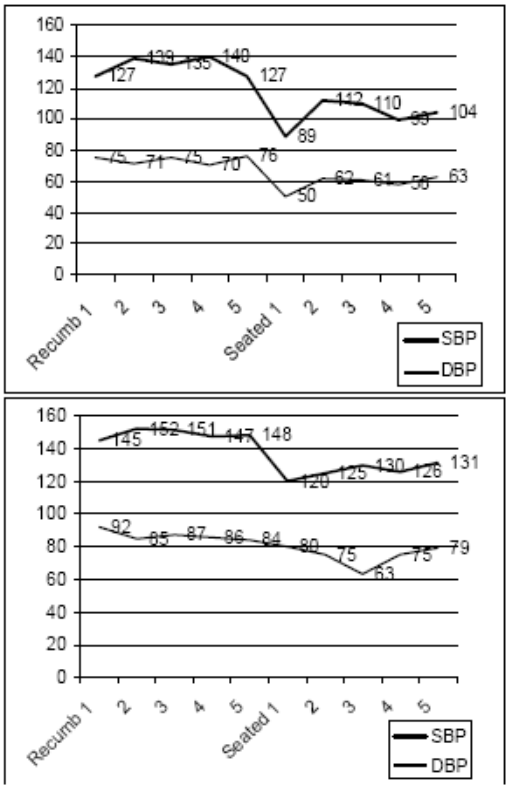

Figure 2. Supine-to-sitting orthostatic test in a patient with supine hypertension and OH. A. Early after sitting up OH occurred; inadvertently the night-time transdermal nitroglycerin patch has not been removed. B. Test repeated after removal of the nitroglycerin patch: OH prevented.

Learning points:

- OH associated with supine hypertension entails the double threat of orthostatic syncope and hypertensive complications.
- The treatment is demanding and the patient's and caregiver's understanding and compliance are essential for success.

Case 3 - postprandial hypotension A 65-year-old man was transferred to our ward for treatment of severe deconditioning that developed after surgical repair of an inguinal hernia. The patient's history included Parkinson's disease, benign prostatic hypertrophy, hypothyroidism and pulmonary embolism. Supine hypertension associated with OH was diagnosed a few years ago. There was progressive cognitive decline. Current medications were carbidopa/levodopa 25/100 mg x 3, rivastigmine 12 mg, midodrine 17.5 mg, fludrocortisone 0.2 mg, clozapine 25 mg, tamsulosin 0.4 mg, levothyroxine 100 mcg per day and warfarin. He weared compression bandages on the calves and thighs while erect. A nitroglycerin 10 mg patch was attached to the skin while supine. At the time of admission to the geriatric ward the temperature was 36.2°C, the heart rate 74 bpm, the respiratory rate 18 breaths per minute, the supine BP was 160/94 mm Hg, and the oxygen saturation 92% on ambient air. On supine-to-sitting orthostatic test the BP decreased progressively from

150/100 mmHg to 120/92 mmHg, yet the patient remained asymptomatic. On the following day, with the patient secured in a geriatric stretch chair, the test was repeated combined with postprandial BP measurements at 10 minute intervals. In the postprandial period the patient fell in an apparently comfortable doze, while his BP dropped to unsafe levels for a long period of time; recovery was spontaneous (Figure 3).

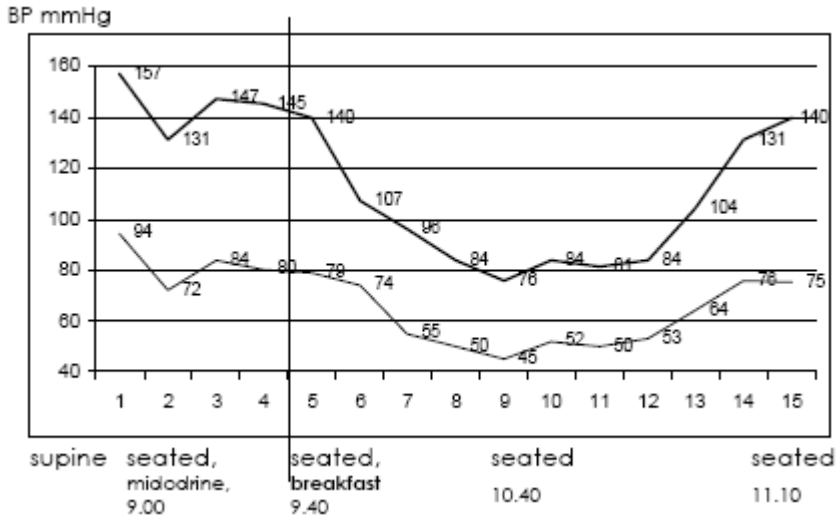

Figure 3. Postprandial BP measurements at 10 minute intervals with the patient seated, immediately in continuation of a supine-to-sitting orthostatic test. Severe and lasting postprandial hypotension occurred.

This case illustrates that patients and caregivers may be unaware of postprandial hypotension unless the BP is measured before and after eating. Our patient was advised to drink 500 ml water before breakfast and lunch and avoid sitting after meals for prolonged periods. He was encouraged to walk after meals, but this was a difficult task to the patient for the time being, so he was advised to lie semi-recumbent for 90 minutes after the meals [56]. It has been recently shown that alpha-glucosidase inhibitors are effective in the treatment of postprandial hypotension [70,71]. In considering the limited experience with Voglibose (the more potent among alpha-glucosidase inhibitors) as well as the risks of polypharmacy in this patient, we postponed the option of this treatment.

Another concern in our patient was prostatic hypertrophy and impaired voiding that was treated with tamsulosine, a blocker of the prostatic α1a adrenoceptor. Blockade of the prostatic α1a adrenoceptors results in relaxation of prostatic smooth muscle and decreases urethral resistance, an effect widely used in the treatment of patients with prostatic hypertrophy. Yet, an adverse effect of ά1 adrenoceptor antagonists is OH, which is reported to occur less frequently on tamsulosin treatment (the drug our patient was receiving) than with alfuzosin, doxazosin and terazosin [72,73].

The α1 adrenoceptor also plays a key role in BP regulation. Midodrine acts as a selective peripherally-acting α1-adrenoceptor stimulant, so midodrine was provided to our patient for the treatment of OH [74,75]. The α1 adrenoceptor agonist midodrine and the α 1

adrenoceptor antagonist tamsulosin bind to adjacent ligand sites and operate through the same signaling pathway [76]. Hence, midodrine and tamsulosin could offset each others pharmacologic activity: tamsulosine enhancing OH [77] and midodrine hindering tamsulosin's activity on the prostate. We felt that combined treatment with tamsulosin and midodrine is unscientific, but could not find mention in the literature on tamsulosine-midodrine interaction or contraindication of their simultaneous use.

Though difficulties in treating our patient seemed unsolvable, improvement occurred within a period of three weeks. The patient was again able to walk for 10 minutes or longer, his BP supine was around 150/88 mmHg, the seated BP and postprandial BP were in the order of 120/80 mmHg, and he was weaned from the urinary catheter.

Learning points:

- Postprandial hypotension is prevalent but often undiagnosed in frail elderly subjects.
- A walk after the meal may attenuate the postprandial hypotension.
- Alpha-glucosidase inhibitors are a promising treatment for postprandial hypotension.

Case 4 - micturition syncope A 77-yr-old man presented after two recent episodes of syncope that occurred at night, after urinating in upright position. One of these events was witnessed by the patient's spouse who described him lying motionless, unconscious, pale and quiet. Shortly afterward, brought to the emergency room, the BP was 140/80 in recumbence and 120/74 while standing. Neurological examination was unremarkable. The patient’s medical history was notable for type II diabetes mellitus, arterial hypertension, benign prostatic hypertrophy, chronic renal failure and dysthymic disorder. During the last 7 years he suffered from dizziness that occurred instantly after rising from bed, lasted a few seconds, and was never followed by a fall, motor disturbance or loss of consciousness. Previous investigations included duplex carotid ultrasonography, carotid sinus massage, cerebral computed tomography, 24 hours electrocardiographic monitoring, transthoracic echocardiogram, and evaluation by a vertigo specialist were all unremarkable. His current medications were enalapril 20 mg, amlodipine 5 mg, venlafaxine 75 mg, omeprasol 20 mg and alfuzosin 10 mg per day. On examination, his body habitus was normal, the temperature 36.7°C, the heart rate 62 bpm. Neurological examination showed peripheral sensory neuropathy. Supine-to-seated and supine-to-standing orthostatic tests with intermittent measurements at 1 minute interval repeatedly showed normal reactivity. Postprandial BP monitored for 45 minutes showed variation by less than 10 mmHg. The Valsalva ratio was 1.04 and heart rate changed on deep respiration by 2 bpm. Bladder voiding was uneventful with minimal residual volume. He was prescribed elastic stockings to put on before going to the toilet, especially at night. The dose of venlafaxine was decreased, other medications were continued. During two months of follow-up no further syncopal spells occurred. The diagnosis of micturition syncope was posited, to be responsible for the two recent syncopal spells. 'Immediate OH' was suggested as the possible explanation for dizziness occurring immediately after standing up.

Micturition syncope is a variant of reflex-mediated situational syncope occurring during or shortly after micturition [78]. Its pathophysiology is likely multifactorial: vagal stimuli associated with micturition, Valsalva's maneuver leading to decreased venous return, a reflex

related to sudden decompression of the bladder and leading to sympathetic nervous withdrawal, as well as a synergistic influence of preexisting OH and a vagal reflex on the BP and heart rate. In a large proportion of patients the cause of syncope cannot be revealed [79-81]. Kapoor et al. described a group of 25 older patients, mostly women, with multiple medical problems and micturition syncope. In this study no cause for micturition syncope could be found, but 88% of the patients had OH. With therapy directed at improving orthostasis there were no recurrences of micturition syncope over a mean follow-up of 15.3 months [78].

The association of micturition syncope with OH in Kapoor's study and our patient's clinical problem may only apparently be similar. In fact, 'early OH' (classical OH) was documented in the former, but not detectable in our patient though tested under various circumstances and repeatedly, taking in account the possible variability of OH [52,55]. 'Initial OH', that occurs within 15 s after standing up is a possible diagnosis to be considered in our patient [34]. However, 'initial OH' is very short lived and therefore probably not accountable for micturition syncope, which occurred after the patient went along the floor to the bathroom, terminated voiding and only than fainted.

For evaluation of patients presenting with micturition syncope a flexible approach has been proposed [82]. In case of a single episode which occurred in a patient who has no overt heart disease, there is no suggestion for exhaustive investigations. Instead, correction of potentially reversible contributing factors, such as volume depletion or excessive medication, together with close follow-up is recommended. In patients with an underlying structural heart disease, even a single episode of syncope should stimulate investigation for possible cardiac causes, in spite of the unmistakable setting of micturition syncope. Patients with structural heart disease or multiple episodes of micturition syncope may benefit from electrophysiological evaluation to clarify the potential mechanism of syncope. Our patient had recent cardiac evaluation that showed no abnormalities.

Learning points:

- Micturition syncope is a variant of reflex-mediated situational syncope.
- The underlying mechanism of micturition syncope is often OH and therapy directed at improving OH is effective to prevent micturition syncope.
- In a large proportion of patients the cause of syncope cannot be revealed.
- A variety of disorders can masquerade as micturition syncope.

V. Symptomatic vs. Asymptomatic OH

The occurrence of orthostatic symptoms, largely representative of inadequate central nervous system perfusion with a fall in blood pressure, depends not only on the magnitude of the BP decline upon assuming upright posture but also on a number of other factors. Cerebrovascular autoregulation acts as a safeguard to protect the brain against excessive oscillations of BP. In the average individual under normal physiologic conditions, changes in mean arterial BP between 60 and 160 mmHg produce little or no change in cerebral blood flow [83]. Thus, cerebral arterioles dilate as mean arterial BP decreases and constrict as mean

arterial blood pressure increases. Beyond these limits of autoregulation, cerebral blood flow is directly proportional to mean arterial BP and is 'pressure-passive'. A sudden decrease in cerebral blood flow occurs at the lower limit of autoregulation. The limits of cerebral autoregulation, and hence susceptibility to orthostatic symptoms, can be affected by a number of conditions. For example, in chronically hypertensive adults, the autoregulatory curve is shifted to the right. Therefore, while in otherwise normal individuals orthostatic symptoms may appear with a drop in the mean BP below 60 mmHg, in hypertensive patients a less drastic drop in BP may be accompanied by symptoms. In more acute conditions (for example ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage and post ictally), cerebral blood flow may become temporarily pressure passive, thus augmenting effects of OH on cerebral blood flow [84]. In addition, hypercapnia ($PaCO_2$ >60 mmHg) [85] as well as hypocapnia ($PaCO_2$ <25 mmHg) may consistently impair cerebral autoregulation [86,87] and distort the correlation between symptoms and OH. Hence, orthostatic symptoms do not necessarily correlate with absolute BP levels.

The minimum BP drop causing orthostatic symptoms differs among patients, expression of an individual susceptibility to orthostatic BP decline. It has been proposed that symptoms induced during a decrease in BP but not fully meeting the definition for OH should still be considered expressions of possible OH [17,19]. The Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (the JNC 7 report) stated that a 10 mmHg systolic BP drop should be regarded as clinically relevant when it is associated with symptoms [19].

Orthostatic symptoms may correlate also with the rate of BP change. Thus, in a study of 400 patients who had head-up tilt test for evaluation of nonspecific dizziness, the feeling of dizziness on tilt occurred uniformly only in patients in whom OH criteria were met within 3 minutes, while barely 25% of patients having a more gradual decrease in BP complained of dizziness [88].

However, orthostatic symptoms are not specific for OH. Similar symptoms may be induced by postural change without a drop in BP and be occur in the context of a panic attack, occult hyperventilation, cerebrovascular disease or postural tachycardia syndrome [87,88-90]; so much so that in a study there was no significant correlation between orthostatic symptoms and evidence of OH [91]. Thus, on the one hand, orthostatic symptoms may occur in the absence of measurable OH and, on the other hand, genuine OH may be asymptomatic.

According to the 1996 consensus definition, OH is diagnosed when a fall in systolic BP of at least 20 mmHg and or diastolic BP of at least 10 mmHg within 3 minutes of standing is recorded. The elements of orthostatic BP drop that are relevant to the definition of OH include the magnitude of the drop, time to reach the BP difference defined as OH, and reproducibility of the orthostatic BP drop. In each of these elements, there exist issues that argue for modification of the presently accepted criteria of OH. Additional questions need to be addressed: Should one standard orthostatic test be applied to different patient populations or should tests be tailored to the patients' clinical circumstances? Are different OH thresholds relevant to various clinical settings, etiologies of OH and comorbidity? Which test has the best predictive power of morbidity and mortality?[21]

Conclusions

Strict adherence to guidelines in evaluation and treatment of OH is worthwhile. Enhancing clinical skills as well as introducing new diagnostic modalities and medications may well improve the quality of life of patients with OH.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter III

Normotensive Shock in the Elderly

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Shock is a severe medical condition serious medical condition that results from a profound and widespread reduction in effective tissue perfusion leading to cellular dysfunction and organ failure [1]. Hypotension, i.e. systolic blood pressure <90 mmHg, or mean blood pressure <60 mmHg, occurs in most patients with shock [1,2]. However, early in the development of shock, hypotension may only be relative to the patient's baseline blood pressure [3]. Indeed, shock may occur without a dramatic fall of the blood pressure (BP), which may remain within the normal range throughout the course of shock, with systolic BP >90 mmHg, >100 mmHg or even higher [1,4-7]. Low systemic perfusion leading to cellular dysfunction and organ failure are characteristic for shock, while arterial hypotension is not a mandatory for the diagnosis. With the onset of hemodynamic dysfunction, compensatory mechanisms attempt to maintain effective tissue perfusion, and many of the manifestations of shock represent the body's attempt to counter the hemodynamic abnormalities. Hence, clinical manifestations of shock are variable; they depend on the nature of the initiating cause, the severity of tissue ischemia as well as the response of multiple organs and systems [1,2].

Elderly patients are at increased risk to develop shock [8]. The diagnosis of shock may not be immediately evident in elderly patients because the diversity of clinical manifestations and because shock may develop with normal BP [1,7,9].

Learning points:

- The most common clinical manifestations of shock are hypotension and evidence of inadequate tissue perfusion.
- Systolic BP <90 mmHg occurs in most patients.
- However, shock may occur without a dramatic fall in BP, which may remain within the normal range during the course of shock.

Pathophysiology

Over 30 years ago, Weil and Shubin distinguished between hypovolemic, cardiogenic, obstructive and distributive shock. The first three categories are characterized by decreased cardiac output leading to diminished perfusion in various organs, and subsequent anaerobic tissue metabolism. On the contrary, in septic shock the cardiac output is normal or increased; it is microcirculatory dysfunction which causes diminished organ perfusion and anaerobic tissue metabolism [10]. A simplified scheme of the pathophysiology of shock is shown in Figure 1.

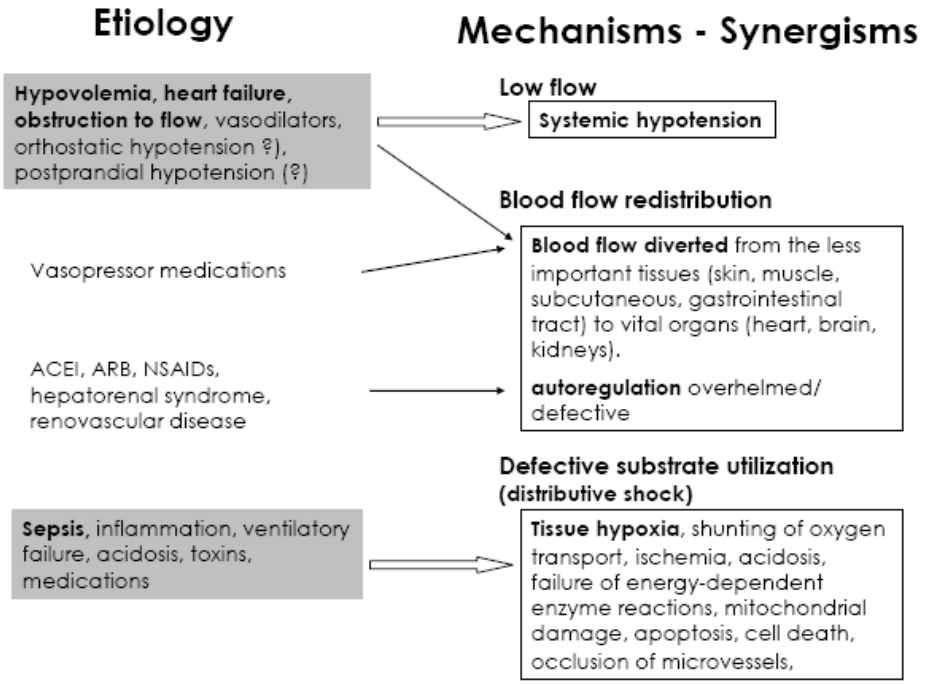


Figure 1. Pathophysiology of shock.

In the microcirculation, inadequate tissue perfusion and resultant hypoxia lead to increasing dependence on anaerobic glycolysis. Intracellular acidosis ensues. Under hypoxia, mitochondrial dysfunction results in inadequate delivery of energy, which causes failure of energy-dependent ion transport pumps, and inability to maintain normal transmembrane gradients of potassium, chloride and calcium. The consequence is a vicious circle of worsening mitochondrial dysfunction, abnormal carbohydrate metabolism and failure of energy-dependent enzyme reactions [11-13]. Cellular ischemia and intracellular calcium accumulation result in formation of xanthine oxidase, which can oxidize purines with the formation of the highly toxic superoxide radical. These reactive oxygen products can inactivate proteins, damage DNA, induce lipid peroxidation of cell membranes, and lead to cell lysis and tissue injury [14].

Furthermore, inadequate tissue perfusion may induce adhesion of leukocytes and platelets to the endothelium, sludging of leukocytes in the microcirculation, activation of the

coagulation system with fibrin deposition and occlusion of small blood vessels. Decreased red or white cell deformability may aggravate the microvascular dysfunction and shunting of the blood circulation around occluded vessels may further decrease delivery of oxygen to tissues. The permeability of small blood vessels may be altered by vasoactive mediators, activated leukocytes, and damaged endothelial cells, so amplifying extravasation of fluid and generating tissue edema. This fluid accumulation may further worsen organ dysfunction [15]. The effects of inadequate tissue perfusion are initially reversible, but prolonged oxygen deprivation leads to derangement of critical biochemical processes and irreversibility; cell death may ensue, end-organ damage, failure of multiple organ systems, and death. Therefore, prompt recognition of shock is critically important [1].

With the onset of hemodynamic dysfunction, compensatory mechanisms attempt to maintain effective tissue perfusion. The compensatory responses in shock are aimed to maintain mean circulatory pressure, maximize cardiac performance, redistribute perfusion to the most vital organs, and optimize the unloading of oxygen to tissues. These effects are produced by stimulation of the sympathetic nervous system, release of hormones (angiotensin II, vasopressin, epinephrine, and norepinephrine), and creation of a local tissue environment that enhances the unloading of oxygen to tissues [2].

Similar compensatory mechanisms are engaged in congestive heart failure. So, chronic reduction in cardiac output is accompanied by a number of adaptative responses, the most prominent among them being the increased activity of the sympathetic nervous system, renin-angiotensin-aldosterone system, and increased secretion of vasopressin [16-18], whereby blood is diverted from the skin, subcutaneous, muscle and gastrointestinal tract to vital organs – the heart, brain and kidneys; such redistribution of the blood flow can restore the ventricular filling pressure. There is, however, a limit to the usefulness of these compensatory mechanisms. Additional decline of stroke volume and excessive activation of the sympathetic nerve endings leads to uncontrolled vasoconstriction [16,18] and tissue ischemia. Thus, an *increased susceptibility to development of shock* may exist in patients with chronic heart failure, since any additional hemodynamic challenge may exhaust the remaining functional reserve and compromise tissue perfusion.

Most vulnerable to ischemia in shock are the mesenteric and renal circulation. Mesenteric vessels constrict disproportionably compared to systemic vessels because of their hyperresponsiveness to angiotensin II [9,16,19]. Renal arterioles, also, constrict disproportionably compared to systemic vessels in shock, as demonstrated by the greater decrease in renal blood flow compared to decrease in BP [20-22]. The salient feature of the renal response to a drop in perfusion pressure is autoregulation, i.e. maintenance of normal blood flow and glomerular filtration rate, even with mean arterial pressure as low as 80 mmHg [23]. Autoregulation during a decrease in renal-artery pressure derives mainly from a decrease in afferent glomerular arteriolar resistance, mediated primarily by prostaglandins. This decrease in afferent resistance sustains glomerular capillary pressure, the driving force of filtration. Glomerular capillary pressure is also supported by the increase in efferent glomerular arteriolar resistance, mediated largely by angiotensin II. However, when renal perfusion pressure drops below the autoregulatory range, endogenous vasoconstrictors increase the afferent arteriolar resistance; this lowers the glomerular capillary pressure and the glomerular filtration rate, resulting in (functional) prerenal azotemia [24-27]. The blood

flow in the postglomerular capillary bed, which perfuses the renal tubules is also reduced, but the tubules remain in the short term intact. With increasing severity and duration of ischemia, structural tubular injury ensues; sloughed tubular epithelial cells and brush-border–membrane debris form casts that obstruct renal tubules; glomerular filtrate leaks back from the tubular lumen across denuded tubular walls into capillaries; finally acute tubular necrosis develops [25-28].

An increased susceptibility to modest reductions in renal perfusion pressure may be observed when renal autoregulation is impaired [1]. This phenomenon has been observed with predilection in the following circumstances: 1) in elderly patients, with atherosclerosis, hypertension, or chronic renal failure [24,29]; 2) in chronic kidney disease when afferent arterioles of functioning glomeruli become dilated, the filtration rate increased to the maximum, unable to further dilate in low-perfusion states [30]; 3) under treatment with nonsteroidal anti-inflammatory drugs, which antagonize the effects of vasodilatory prostaglandins on renal afferent arterioles, causing increased resistance to flow, lowering the glomerular capillary pressure and decreasing the glomerular filtration [31,32]; 4) under treatment with angiotensin converting enzyme inhibitors, which interfere with angiotensin II action on efferent arteriolar resistance, causing the glomerular capillary pressure to diminish and glomerular filtration to decrease [29,33]. Within the mesenteric circulation, even a moderate degree of intestinal ischemia that is not sufficient to cause mucosal necrosis, may cause damage to the intestinal epithelial barrier (20). Once this barrier is compromised, the absorption of bacteria, endotoxin, digestive enzymes, and other noxious intestinal contents, may injure various organs and result in ‘multiple system organ failure’ [34].

In septic shock, inflammatory mediators are a major cause of cell injury [35-37]. Inflammatory cytokines, especially tumor necrosis factor (TNF) and interleukin-1 (IL-1), can produce dysfunction of transmembrane ion gradients similar to that described with cellular ischemia. In addition, TNF can stimulate the release of other cytokines, platelet-activating factor, leukotrienes, prostaglandins, and thromboxane. These mediators may exert their influence on the vasculature to produce inadequate perfusion, or may produce direct injury to cells in a number of organs. In sepsis endothelial cells are less responsive to vasoactive agents, loose their anionic charge and normal glycocalyx, become leaky and give rise to massive over-expression of nitric oxide. Disturbed gap junctions disrupt intercellular endothelial communication and thus regulation [36]. Tumor necrosis factor, released from monocytes and macrophages in underperfused tissues, depress myocardial contractility [38,39] and could be one among many factors perpetuating shock.

Clinical Manifestations of Shock

Inadequate tissue perfusion in shock may cause a variety of systemic and organ manifestations. Many of the clinical symptoms of shock are manifestations of the body's attempts to maintain adequate tissue perfusion. Other symptoms are expressions of organ ischemia and failure: symptoms of encephalopathy (ischemic or septic, cortical necrosis), cardiac symptoms (arrhythmia, ischemia, myocardial depression), respiratory failure, ischemic nephropathy, gastrointestinal symptoms (ileus, erosive gastritis, pancreatitis,

acalculous cholecystitis, colonic hemorrhage), 'shock liver', disseminated intravascular coagulation, hyperglycemia, late hypoglycemia, immune depression, and depression of the gut barrier function [1,40]. Mild symptoms and impairment of one or a few organs may occur in early phases of shock. Multi-organ failure is typical for advanced shock.

We use to classify shock based on the leading clinical symptoms: 1) hypotensive or normotensive, 2) cold (cutaneous vasoconstriction) or warm (typically septic shock), 3) with single organ or multi-organ damage.

Normotensive Shock

Ischemic acute renal failure and/or shock liver may occur without a dramatic fall of the blood pressure (BP), which may remain within the normal range throughout the course of shock, with systolic BP >90 mmHg or even higher [1,4-7]. Recently, normotensive shock came in focus in recognizing the importance of normotensive ischemic acute renal failure and normotensive shock liver [1,9].

Patients with *ischemic acute renal failure* typically have low systemic perfusion, sometimes caused by volume depletion, although their BP may not fall dramatically [1]. Blood urea nitrogen (BUN) to creatinine ratio of 20:1 or higher strongly suggest the presence of renal hypoperfusion, even with the BP in the normal range. Two forms of ischemic acute renal failure are familiar to clinicians - prerenal azotemia and acute tubular necrosis [41,42]. The importance of addressing even mild renal failure is illustrated by a study showing that hospitalized patients with a modest increase in the serum creatinine level (0.3 to 0.4 mg/dL) have a 70% greater risk of death during the current admission than persons without any increase in creatinine [43].

Serum creatinine and creatinine clearance, commonly used to evaluate and monitor renal function, are relative insensible and late markers of renal damage. Recently, assessment of urinary enzymes and urinary low molecular weight proteins has been introduced in hospital practice as early markers of renal damage. Two pathological mechanisms are responsible for increased enzymuria or microproteinuria [44]. First, injured tubular cells release enzymes and microproteins from the cytosol into the tubular lumen, resulting in increased enzymuria and microproteinuria. Second, low molecular weight proteins which are freely filtered across the glomerular capillary wall and are almost completely reabsorbed by the proximal tubular cells, cannot be appropriately reabsorbed when tubular cells are damaged; so pathological microproteinuria ensues. Pathological enzymuria and microproteinuria can be induced by a mild and reversible dysfunction of the tubular cells, and is not necessarily associated with a necrotic irreversible damage. Remarkably, pathological enzymuria occurs long before the increase of serum creatinine [45].

Learning points:

- Autoregulation of renal blood flow maintains normal flow and glomerular filtration rate, even with mean arterial pressure as low as 80 mm Hg.
- When renal autoregulation is impaired, there may be an increased susceptibility to modest reductions in renal perfusion pressure.

- This phenomenon may be seen in elderly patients, with atherosclerosis, hypertension, chronic renal failure, or congestive heart failure
- Medications that may interfere with autoregulation of renal blood flow are nonsteroidal anti-inflammatory and angiotensin converting enzyme inhibitors

Shock liver, also known as ischemic hepatitis or hypoxic liver injury, is defined as a massive and transient increase in serum transaminase levels due to an imbalance between hepatic oxygen supply and demand, in the absence of other causes of acute liver damage [9]. Precipitating factors are pulmonary edema, tachy-arrhythmias, sepsis, and severe hypoxemia [46-48]. Predisposing factors are advanced age, chronic heart failure, and chronic liver congestion. With low cardiac output the hepatic blood flow is reduced. Redistribution of blood flow to vital organs further shortens the hepatic fraction of blood supply [16-18]. Stagnation of blood in the liver secondary to right heart failure curtails hepatic perfusion and generates hypoxia [46]. Elderly patients with chronic congestive heart failure are particularly prone to development of hypoxic liver injury when perfusion decreases [9,47,48]. Remarkably, shock liver may occur in the absence of arterial hypotension [46-48]. The treatment and prognosis of shock liver depend on the underlying disease [9,49]. Characteristically, transaminase levels which are elevated 20-fold or more at onset will normalize over a few days [9].

Combined shock liver and shock kidney, like isolated shock liver, may occur in the course of chronic heart failure as an acute complication. Like isolated shock liver, combined shock liver and shock kidney may occur in the absence of arterial hypotension. A clinical case study was conducted 20 years ago at our ward of internal medicine, to describe the characteristics of 'cardiogenic hepatic injury – renal impairment', thus extending our earlier experience [7,49]. Twenty-five patients were studied prospectively during a 15-year period. There were 18 males and 7 women, their median age was 78 years (range 63 to 94). Chronic congestive heart failure was diagnosed in all, with NYHA classes III or IV in 21 patients. Pulmonary edema preceded to hepatic injury and renal impairment by 24 hours or less in 21 patients and an acute coronary event in 3 patients. No overt arterial hypotension, i.e. systolic BP below 90 mmHg or decrease of the systolic BP by 40 mmHg or more of baseline, was observed; the possibility of alcoholic, viral or drug-induced hepatitis was excluded. During the course of 'cardiogenic hepatic injury – renal impairment', the peak values of AST were median 988 U/dL (normal <40 U/dL), prothrombin INR median 1.8, serum creatinine 2.4 mg/dL and BUN median 48 mg/dL. Renal impairment was of functional nature, characterized by normal urinary sediment and BUN/creatinine ratio 20:1 or more. Fifteen patients died during the current admission, a median 4 days after occurrence of 'cardiogenic hepatic injury – renal impairment'. Among survivors, the median time to return to baseline of the laboratory abnormalities was 4.3 days.

Elderly Subjects Are at Increased Risk of Shock

Aging is associated with a range of changes of cardiovascular structure and functioning [50,51].The heart becomes slightly hypertrophic, the aorta and major elastic arteries become

elongated and stiffer with increased pulse wave velocity, there is evidence of endothelial dysfunction, and the arterial baroreceptor control of the heart rate is altered. Poor baroreceptor-mediated BP responses may impair the moment-to-moment adjustments of sympathetic nerve activity and peripheral vascular resistance, with increased propensity to postural or postprandial hypotension.

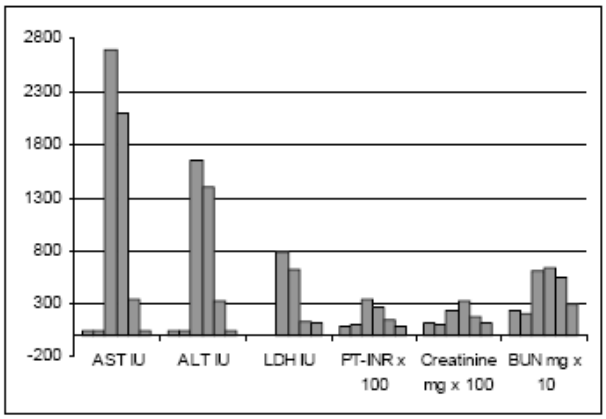
Cardiopulmonary reflexes, which are involved in extracellular fluid homeostasis, are impaired in the elderly thus predisposing to dehydration; this may demand caution in prescribing diuretic therapy in the elderly [50]. Aging is also associated with impaired paracrine responses in the kidney. Aging-associated changes in renal function do not cause significant disturbances under normal conditions, but under stressful situations, particularly when adrenergic activation is present, the kidney may become vulnerable [8]. Therefore it is not surprising that normotensive shock kidney and shock liver, alone or in combination, have been described mostly in elderly subjects [1,7,9].

Case Histories

Recognizing that shock may occur in the absence of arterial hypotension may aid, in certain ambiguous situations, to elucidate the cause of an obscure organ damage. The following case histories illustrate such situations.

Case 1 - cardiogenic hepatic injury and renal impairment. A 74-year-old man was suffering from progressive disability due to heart failure and anginal syndrome over the past 16 years. He has been hospitalized several times because of pulmonary edema, and this was also the cause of his present admission. The patient's medical history was notable for treated hypertension and dyslipidemia, moderate alcohol use, and he accumulated 72-pack-years of tobacco use before quitting 10 years ago. Transthoracic echocardiography showed left ventricular enlargement; the left ventricular ejection fraction was 25%; there was moderate mitral and tricuspid regurgitation. Thallium myocardial scan showed cold spots, appearing on baseline and unchanged under dipyridamole challenge. The patient had declined to undergo coronary catheterization. Current medications included aspirin 100 mg/day, carvedilol 25 mg/day, ramipril 5 mg/day, furosemide 80 mg/day, spironolactone 12.5 mg/day and simvastatin 20 mg/day. In the emergency room, the BP was 150/98 mm Hg and the pulse rate 98/bpm. Cardiac examination revealed sustained apical impulse, S3 and S4 heart sounds, grade 3/6 systolic murmur best heard at the apex. The jugular venous pressure was elevated up to the angle of the mandible with the patient sitting at a 45-degree angle and hepatojugular reflux was elicited. There were inspiratory crackles in the lower lung fields. Bilateral 2+ pitting edema was present. Chest radiography showed cardiomegaly, right-sided pleural effusion, and confluent airspace densities with a perihilar and lower lung zone distribution. Electrocardiography showed left atrial enlargement and left ventricular hypertrophy with secondary ST-T changes. The troponin I levels at arrival and 12 hours later were normal (<0.1 0.7 ng/mL). The patient received oxygen delivered through a face mask, intravenous furosemide 80 mg, morphine sulfate 4 mg and transdermal nitroglycerin 10 mg. The pulmonary edema remitted and the patient was admitted to the medical ward. The regular medications were continued. On the third hospitalization day he had another episode of

pulmonary edema, treated effectively with furosemide and morphine. The BP was 142/90 mmHg, the electrocardiogram showed sinus tachycardia and the troponin I level was normal again. A few hours later the patient's clinical condition had improved, the BP was normal, but laboratory tests showed marked impairment of hepatic and renal functions (Figure 2). The BUN/creatinine ratio was 22. The urinary sediment was unremarkable. Ramipril was temporarily discontinued. During the following three days the hepatic and renal tests returned to their initial levels, the patient remained hemodynamically stable and was discharged after 11 day of hospitalization. Four months later, another episode of pulmonary edema occurred and was treated in a similar way, without development of hepatic and renal impairment.



Day	0	1	2	3	4	7
AST IU	32	45	2700	2100	338	34
ALT IU	36	40	1650	1400	320	40
LDH IU			790	620	124	120
PT-INR	0.9	0.92	3.4	2.7	1.4	0.9
Creatinine mg/dl	1.1	1	2.4	3.2	1.7	1.2
BUN mg/dl	23	21	61	63	55	30

Figure 2. The course of normotensive shock liver and shock kidney in Case 1.

Based on the close temporal relationship between the precipitating cardiac decompensation and subsequent hepatic and renal damage, which are similar to well-recognized cardiogenic end organ damage in shock, and in the absence of other etiologies (the possibility of alcoholic, viral or drug-induced hepatitis were excluded), our diagnosis was *normotensive shock caused by heart failure*. While the cardiac etiology was obvious, the emergence of the syndrome was, nevertheless, unpredictable. In this patient having suffered numerous episodes of pulmonary edema, the duration and the apparent severity of pulmonary edema did not predict which episode will be followed by shock liver and shock kidney.

Case 2 – shock kidney with normal BP. A 72-year-old man was diagnosed by gallium scan and computerized tomography with L1-L2 discitis. He has been in poor health for several years, with a history of arterial hypertension, myocardial infarctions, diabetes mellitus type II, dyslipidemia, and mild renal failure. He had several episodes of cardiac

decompensation. Six months ago he underwent an emergency femoro-popliteal artery bypass operation, which complicated with methicillin resistant staphylococcus aureus (MRSA) wound infection. Antibiotic treatment was of no avail and, eventually, below knee amputation was carried out. Subsequently the fever remitted and the white blood cell count and C reactive protein returned to normal values. However, low grade fever arised associated with loss of appetite and low back pain. On physical examination, the patient was cachectic, the BP 182/84 mmHg, the heart rate 76 bpm, respirations 16 per minute. A grade 3/6 pansystolic murmur was heard over the ventricular apex. There was hepatojugular reflux and grade 1 ankle edema. Laboratory tests were remarkable for C reactive protein 230 mg/L, serum creatinine 1.6 mg/dL, albumin 2.8 g/L. MRSA was recovered in 3 consecutive blood cultures. Imaging studies lead to the finding of vertebral osteomyelitis. Transesophageal echocardiography showed diffusely diminished contractility of the left ventricle, the left ventricular ejection fraction was 30% in the presence of moderate mitral regurgitation and pulmonary hypertension; no valvular vegetations were detected. The estimated creatinine clearance according to the Modification of Diet in Renal Disease (MDRD) equation was 45 mL/min/1.73 m^2 and according to Cockcroft-Gault equation was 30 mL/min/1.73 m^2. Treatment with intravenous vancomycin 1 g once at 24 hour intervals was administered. Vancomycin trough levels were measured twice per week and were found satisfactory, between 5 and 8 μg/mL. The patient continued to receive his current medications, including aspirin 100 mg/day, carvedilol 12.5 mg/day, ramipril 5 mg/day, furosemide 40 mg/day, spironolactone 12.5 mg/day, simvastatin 20 mg/day and insulin.

Thirty days on vancomycin treatment, the temperature was normal, the C reactive protein decreased to 18 mg/L. However, the signs of heart failure worsened, with generalized edema and pulmonary congestion. Laboratory tests were unchanged. Furosemide i.v drip 160 mg per day was administered. Six days later the serum creatinine had risen to 3 mg/dL and the BUN to 110 mg/dL. The urinary sediment was unremarkable. The AST, ALT and prothrombin time remained within the normal range. There was essentially no change in the patient's BP, varying as before between 124-160/70-82 mmHg. The BUN to creatinine ratio 30:1 at the time of worsened renal status suggested the presence of renal hypoperfusion. *Normotensive shock kidney* was the tentative diagnosis. On diagnosing the severe deterioration in renal function, the treatment with vancomycin, furosemide and ramipril was discontinued, and rifampicin was instituted. Gradually, over a period of 10 days the creatinine decreased to 2.6 mg/dL and the BUN to 32 mg/dL. Two months later, the patient had recovered from vertebral osteomyelitis, the heart failure and BP were fairly controlled, but the plasma creatinine remained 3 mg/dL.

The patient had numerous predisposing factors known to increase susceptibility to renal hypoperfusion (1): old age, atherosclerosis, chronic hypertension, chronic kidney disease, sepsis, hypoalbuminemia and treatment with an ACE inhibitor. In the context of severe heart failure, the compensatory humoral and neural responses might have been utmost engaged with redistribution of blood flow to vital organs [16], the renal circulation becoming more vulnerable to ischemia. The volume depletion cased by furosemide may have aggravated renal ischemia and vancomycin may have enhanced the predisposition to renal damage. On the other hand, it is well known that elderly persons are at increased risk to develop vancomycin-induced nephrotoxicity, in particular when receiving a loop diuretic, [52,53]. In

a complex clinical situation such as the present case, when numerous pathological influences may have affected the renal perfusion, it may be their joint influence which caused the damage. In fact, the difficulty to distinguish between aminoglycoside, sepsis and hypotension-induced renal injury has been well recognized [52].

The concept of normotensive shock is in line with the definition of shock [1,9]. While Case 1 illustrates the typical situation, the diagnosis of shock is more disputable in Case 2, illustrating the diversity of real life problems. The possible synergism of multiple subliminal influences should be considered in this case.

Protracted Orthostatic Hypotension – Predisposing to Shock?

Orthostatic hypotension is defined as a fall in systolic BP of at least 20 mmHg and or diastolic BP of at least 10 mmHg within 3 minutes of standing [54]. Nevertheless, the onset of orthostatic symptoms occurs in many patients well beyond 3 minutes of standing. Streeten et al. first drew attention to delayed orthostatic hypotension that occurred after 13 to 30 minutes of standing [55]. In a recent study of patients who developed hypotension on tilt the classical orthostatic hypotension which occurs within 3 minutes of head-up tilt was noticed in 46% of subjects, while in other subjects the onset of orthostatic hypotension started later: between 3 and 5 minutes of tilt in 3% of cases, between 5 and 10 minutes in 12%, after 10 minutes of tilt of more in 39% of cases [56]. Analogous to orthostatic hypotension, postprandial hypotension is commonly defined in the literature as a decrease in systolic BP of 20 mmHg or more, that occurs within 2 hours of a meal [57].

Postural hypotension and postprandial hypotension are particularly common in elderly subjects [58,59]. In community dwelling individuals more than 65 years of age, its prevalence is approximately 20%; in those older than 75 years it is as high as 30%. Postural hypotension has been revealed in up to 50% of frail elderly individuals, and in 64% among elderly patients hospitalized for acute conditions [58]. Nearly all elderly persons experience some postprandial decrease in BP; in 24% to 36% of these patients, systolic BP decreases more than 20 mm Hg within 75 minutes of eating a meal [60,61]. Profound postprandial hypotension has been observed in patients with Parkinson disease [57]. There is a high statistical probability that orthostatic and postprandial hypotension occur simultaneously [59].

Dizziness and syncope are typical symptoms related to orthostatic hypotension. The relationship of other symptoms to orthostatic hypotension may not be obvious, unless one is aware of the wider spectrum of orthostatic disturbances. Thus, weakness, fatigue, visual blurring, vertigo, suboccipital and paracervical pain, chest pain on upright posture, headaches, palpitations, or dyspnea may occur [62].

Orthostatic hypotension is set off within a few minutes when the patient lies down or becomes recline by syncope. Such brief episodes of hypotension may not endanger the kidney, liver or other organs. However, moderate orthostatic hypotension may persist for long periods of time and even go unobserved by patients and nurses, unless systematically looked for (Figure 3) [63]. In patients represented under A and B, orthostatic hypotension

was asymptomatic throughout the test. In Case C, dizziness was reported simultaneously with a BP drop consistent with orthostatic hypotension. In Case D, the patient was dizzy before tilt and subsequent orthostatic hypotension had no additional effect on the patient's symptoms.

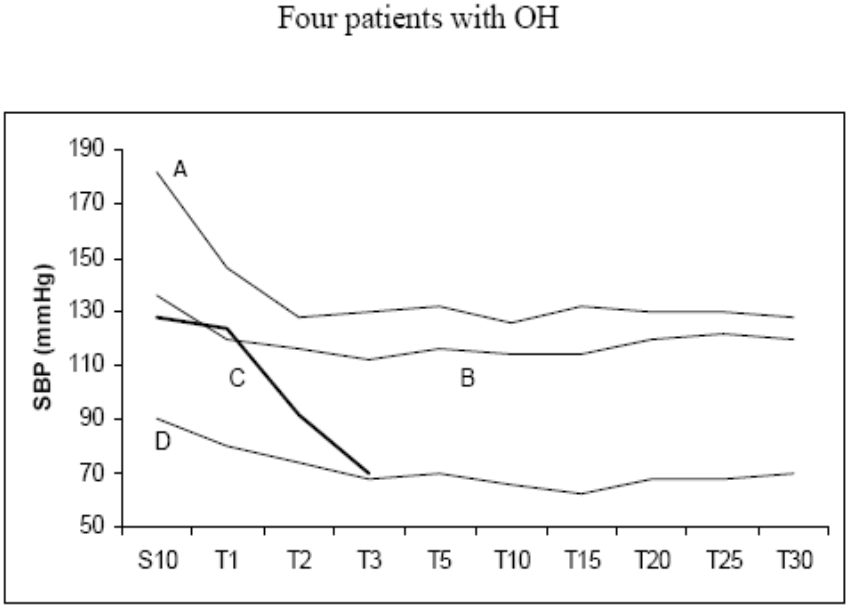


Figure 3. Different length of episodes of orthostatic hypotension (reproduced with permission).

Patients and the patients' caregivers may be unaware of postprandial hypotension unless the BP is measured before and after eating. Postprandial hypotension may be protracted (an hour or longer) and the BP drop may be profound, as illustrate in the case history described in Chapter 2. There is a high statistical probability that orthostatic hypotension and postprandial hypotension occur simultaneously, but postprandial hypotension is distinct from orthostatic hypotension. Unlike orthostatic hypotension, postprandial hypotension may occur in the supine position; postprandial hypotension when occurring while the patient is sitting the hypotension may resolve upon standing up and walking; postprandial hypotension is not alleviated by venous compression therapy [59-61].

The possible role of postural hypotension and postprandial hypotension in initiating shock has not been addressed in the literature. Several issues may be of practical interest: Can prolonged orthostatic hypotension cause hypoperfusion in viscera? What magnitude and duration of orthostatic BP drop are critical to cause harm? What additional predisposing factors must come together so that it occurs? The proposal to perform systematic testing for orthostatic hypotension and postprandial hypotension in high risk elderly patients, as to avoid orthostatic complications [59], may get additional impetus in considering the possible deleterious effects of prolonged, undiagnosed orthostatic hypotension. Finally, may protracted orthostatic hypotension predispose to shock?

Normotensive Shock - Prevention – Diagnosis – Monitoring the Course

Awareness of risk factors is essential for shock prophylaxis. Influences that may impair tissue perfusion, metabolism and oxygenation should be avoided. Two scenarios are not uncommon and should call attention to the risk of developing shock, particularly in frail elderly subjects [1]. In the first, the patient has what turns out to be sepsis, but at the onset does not have fever or any localizing symptoms. In the second, a patient who is receiving diuretics for hypertension or congestive heart failure may have anorexia and stop eating for some reason or may otherwise have decreased salt intake. Progressive negative sodium balance results in volume depletion and a downward drift in tissue perfusion [1]. We call attention to a possible third scenario, involving undiagnosed orthostatic hypotension/ postprandial hypotension.

Clinical signs of poor peripheral perfusion consist of a cold, pale, clammy, and mottled skin, associated with an increase in capillary refill time. Most patients have hypotension, tachycardia, oliguria, and a clouded sensorium. However, clinical signs of shock may be unreliable since hypoperfusion may be masked by compensatory hemodynamic changes. In general, a mean BP less than 60 mmHg in an adult is considered hypotension. However, BP must be evaluated in terms of previous chronic BP readings. A patient with chronic hypertension may experience shock at higher BP values. A decrease of 50 mmHg or more from chronic elevated levels is frequently sufficient to produce tissue hypoperfusion. Conversely, in some patients with chronically low BP, shock may not develop until the mean BP drops to less than 50 mmHg [2].

Global 'downstream' markers of impaired tissue perfusion, such as mixed venous oxygen saturation and blood lactate which are frequently relied upon in practice, are insensitive indicators of tissue hypoxia [64]. Likewise, global hemodynamic parameters fail to provide adequate information on tissue perfusion [65].

Noninvasive assessment of the peripheral perfusion, on the contrary, can allow very early diagnosis of hypoperfusion in the microcirculation [65]. Commonly used optical methods for monitoring the microcirculation are perfusion index, near-infrared spectroscopy, laser Doppler flowmetry and orthogonal polarization spectroscopy. Continuous noninvasive transcutaneous measurement of oxygen and carbon dioxide tensions can be used to estimate cutaneous blood flow [65]. Hypercarbia is a general phenomenon of perfusion failure, which is promptly reversed with restoration of normal blood flow. Sublingual PCO_2 correlates closely with PCO_2 in internal organs. Based on these principles, monitoring of sublingual PCO_2 has been introduced for early diagnosis of circulatory failure. Several studies have demonstrated that sublingual PCO_2 is practical and reliable in the diagnosis of circulatory failure, useful for early diagnosis of shock, an indicator of severity of shock, and also as guidance for fluid resuscitation during shock [66,67]. Application of sublingual PCO_2 monitoring may open the possibility for earlier diagnosis of shock.

Learning points:

- BP and clinical signs of poor peripheral perfusion may be unreliable for early diagnosis of shock, since hypoperfusion may be masked by compensatory hemodynamic changes.
- The tests in common clinical use, mixed venous oxygen saturation and blood lactate, are insensitive indicators of tissue hypoxia and shock.
- Monitoring the microcirculation, on the contrary, can allow very early diagnosis of hypoperfusion.
- Sublingual PCO_2 is a marker of microvascular perfusion and tissue hypoxia which is practical and reliable in the diagnosis of circulatory failure.

Conclusions

Elderly patients are at increased risk to develop shock. In many, shock is caused by the intricate action of subliminal influences, which involve increased susceptibility to modest reductions in perfusion pressure. Because shock may develop while the patient's BP is within the normal range, the diagnosis may be missed. A variety of single-organ or multi-organ manifestations fit into the clinical framework of shock. The principle of 'one organ shock' is an arbitrary matter, but is matching the current definition of shock.

The influences that may impair tissue perfusion, metabolism and oxygenation should be avoided for averting shock in the predisposed. Early diagnosis and treatment of infection and dehydration might prevent shock in the elderly, though additional proof of efficiency of these interventions needs to be provided by future studies.

Application of noninvasive monitoring of the peripheral circulation may open the possibility for earlier diagnosis of shock, in general, and of clinically occult normotensive shock, in particular.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter IV

Diabetes Management in Acute Geriatric Care

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The term diabetes mellitus (DM) describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia. DM is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin. Insulin has a number of effects on glucose metabolism: it increases glucose transport into fat and muscle cells, stimulates glycogen synthesis, and inhibits glycogenolysis and gluconeogenesis. The American Diabetes Association defines DM as (1) a fasting plasma glucose ≥126 mg/dL, (2) a nonfasting plasma glucose ≥200 mg/dL, or (3) an oral glucose tolerance test ≥200 mg/dL in the 2-hour sample; the above laboratory findings needed to be confirmed on a separate day. Beyond the domain of energy metabolism, insulin affects steroidogenesis, vascular function, fibrinolysis and growth.

In human pathology, insulin deficiency and/or insulin resistance are implicated in the pathogenesis of cardiovascular disease, premature death, blindness, renal failure, peripheral vascular disease, fractures, frailty, depression, and cognitive decline. An increase by 1% in glycated hemoglobin level is associated with an 18% increased risk of cardiovascular events [1], 12 to 14% increased risk of death [2,3], and 37% increased risk of retinopathy or renal failure [3].

I. Epidemiology of DM in Geriatric Populations

Advancing age is associated with a relative deficiency of insulin secretion, decreased beta-cell sensitivity to incretin hormones and increased insulin resistance. Impaired beta-cell compensation to age-related insulin resistance in older people may predispose to impaired glucose tolerance and type 2 DM [4]. Indeed, most persons with DM are over 60 years of age

[5]. According to the Third National Health and Nutrition Examination Survey (NHANES II and III conducted from 1976 to 1980 and from 1988 to 1994), the prevalence of type 2 DM in Americans 60-74 years of age was >20% [6-8]. An additional 20% of this population met criteria for impaired glucose tolerance, defined as 2 hours postprandial glucose level ≥140 mg/dL but <200 mg/dL and a fasting blood glucose <126 mg/dL [6]. Similar data were reported form most European countries [8,9]. Among functionally dependent, severe cognitive depressed, elderly, long-term care patients who received enteral nutrition the frequency of DM was 47%, with about half of the cases undiagnosed [11]. Men develop diabetes more commonly than women [12]. The prevalence of DM in the elderly is expected to increase to 44% in the next 20 years [6].

II. Stress-Induced Hyperglycemia

Stress-induced hyperglycemia is common during acute illness and is frequently reported in non-diabetic subjects. Stress causes an excessive release of the counter-regulatory hormones glucagon, epinephrine, cortisol, growth hormone and insulin-like growth factor, as well as overproduction of the inflammatory mediators TNF-α, interleukin-1 and interleukin-6 [13]; each of them acts to increase blood glucose. In turn, hyperglycemia promotes production of more inflammatory cytokines thus sustaining stress-induced hyperglycemia [14]. Traditionally, non-diabetic patients with moderate hyperglycemia were observed without treatment, with the belief that higher glucose levels were protective and belong to the physiological stress response in acute illness [15]. However, there is substantial evidence that hyperglycemia, even at moderate levels and in non-diabetics, is associated with worse outcomes and increased in-hospital mortality [16-19], particularly in elderly subjects [20].

The mechanism of harm from hyperglycemia, i.e. the deleterious effects of hyprglycemia on different homeostatic systems, has been studied in vitro systems and in animal models. Hyperglycemia impairs oxygen radical generation in activated neutrophils and, thereby, intracellular bactericidal activity is weakened [21,22]. Beyond impaired phagocytosis, the deleterious consequences of hyperglycemia on the immune system include glycation of immunoglobulins [23], decreased lymphocytes counts [24], and reduced CD-4 and CD-8 T-cell populations. These effects are reversed when the blood glucose is lowered [25]. Hyperglycemia also exerts pro-inflammatory influences. In humans, elevation of glucose to 270 mg/dL for 5 hours has been associated with increased plasma levels of interleukins IL-6, IL-18, and TNF-alpha [26]; the hyperglycemia-induced rise in IL-6, TNF- alpha, and other cytokines may induce acute inflammation. Furthermore, hyperglycemia may induce endothelial dysfunction [27] and abnormalities in hemostasis predisposing to thrombosis [28]. Hyperglycemia may impair ischemic preconditioning of the myocardium and may increase myocardial infarct size through apoptosis or by exaggerated ischemia-reperfusion cellular injury [29,30].

Hyperglycemic thresholds of harm are not well defined. In vitro trials, a mean glucose plasma level >200 mg/dL causes leukocyte dysfunction [31]. In patients with poorly controlled DM, when the mean fasting blood glucose was reduced from 293 ± 20 mg/dL to 198 ± 29 mg/dL a significant improvement in granulocyte adherence was observed [31].

Hyperglycemia, whether diabetic or stress-induced, is associated on the short term with increased risks of morbidity and mortality [32-35]. On the long-term, stress-induced hyperglycemia may be the herald of DM. Patients with hyperglycemia that was first noticed at the time of hospital admission for acute illness were re-examined one year later, revealing impaired glucose tolerance in 10% and DM in 21.6% of the cases; the latter were subjects who seemingly had stress-induced hyperglycemia but in fact were diabetics [36].

III. Goal Blood Glucose Level

Lowering hemoglobin A1c to an average of 7% has clearly been shown to reduce microvascular and neuropathic complications of diabetes and, possibly, macrovascular disease. Therefore, the American Diabetes Association 2008 guidelines posit the hemoglobin A1c goal for adults <7% [37]. An incremental benefit, though small, has been recorded in epidemiological studies by lowering hemoglobin A1c from 7% into the normal range. Hence, for selected individuals, the hemoglobin A1c goal as close to normal (<6%) is advised with the condition that significant hypoglycemia can be avoided. Less stringent hemoglobin Alc goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, individuals with comorbid conditions, and those with longstanding diabetes and minimal or stable microvascular complications [37,38].

Distinctive glycemic goals for hospitalized diabetic patients have been proposed [39,40], and were recently reconsidered [37]. The American College of Endocrinology Consensus Statement on inpatient diabetes management recommended blood glucose less than or equal to 110 mg/dL for critical care patients, and pre-prandial blood glucose of less than or equal to 110 mg/dL with maximal blood glucose levels of no greater than 180 mg/dL for patients in noncritical care units [39]. Likewise, the American Diabetes Association proposed blood glucose levels be kept as close to 110 mg/dL as possible and generally less than 180 mg/dL for critical care patients; in noncritical care units the American Diabetes Association recommended a pre-prandial blood glucose target range of 90 to 130 mg/dL and maximal blood glucose less than 180 mg/dL [40]. These patients require an intravenous insulin protocol that has demonstrated efficacy and safety in achieving the desired glucose range without increasing risk for severe hypoglycemia. In non-critically ill patients there is no clear evidence for specific blood glucose goals. The 2008 guidelines propose fasting glucose goal <126 mg/dl and all random glucoses <180-200 mg/dl, if these goals can be safely achieved. Insulin is the preferred drug to treat hyperglycemia in most cases [37].

These recommendations are subject of controversy because they extrapolate data from a few randomized trials involving critically ill patients to the larger population of hospitalized patients. Also, the universal benefit of euglycemia in adults requiring intensive care has been questioned. Only one prospective randomized controlled trial has shown a decrease in morbidity and mortality with tight glycemic control in the intensive care unit [41], while more recent trials failed to duplicate the benefits of that trial [42-44]; substantial hypoglycemia has been reported more frequently to occur with therapy attempting tight glucose control. Data of a recent meta-analysis totaling 8432 patients showed that hospital mortality did not differ between tight glucose control (mortality 21.6%) and usual care

(mortality 23.3%; RR, 0.93). Tight glucose control was associated with significantly decreased risk of septicemia (10.9% vs. 13.4%; RR, 0.76) but the risk of hypoglycemia significantly increased (13.7% vs. 2.5%; RR, 5.13) [45]. Another meta-analysis concerned with the effect of perioperative insulin infusion on surgical morbidity and mortality came to comparable conclusions [46]. Hence, the glycemic targets for hospital care proposed in the guidelines [39,40] might be too stringent, and their implementation not devoid of risks [47].

In the outpatient setting, the benefits of intensive glucose control remain uncertain despite earlier promise [40]. A large-scale study identified a previously unrecognized harm of intensive glucose lowering in patients with type 2 DM [48]. 10.251 diabetic patients were assigned to receive intensive therapy (targeting hemoglobin A1c level below 6.0%) or standard therapy (targeting hemoglobin A1c level 7.0 to 7.9%). Of these patients, 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. As compared with standard therapy, the use of intensive therapy for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings lead to reassessment of the target hemoglobin A1c at 7%. Lower individualized targets may be appropriate when the focus is primary prevention of macrovascular disease [49] and less-intense targets (hemoglobin A1c $\leq$ 8%) would be applied to patients with unstable cardiac disease or diminished general health [50,51]. It might be particularly important to control potassium concentrations when hemoglobin A1c is aggressively lowered [50].

Guidelines for treatment of older diabetic patients in the outpatient setting recommended an individualized approach, taking into consideration the patient's approximate life expectancy, the presence or absence of unusually good or poor health and function, geriatric syndromes and the patient's goals and treatment preferences. A central concept is that patients whose life expectancy is less than 8 years are considered unlikely to benefit from intensive glucose control, whereas patients with longer life expectancy are thought to be good candidates for intensive glucose control [52-54]**.** These principles are endorsed by an analysis run on a computer model: the benefits of treating diabetic patients to a hemoglobin A1c level 7% versus hemoglobin A1c 7.9% were evaluated in individuals 60 to 80 years of age. On this model, the advantages of tighter glycemic control decreased as age increased, supporting the easing the hemoglobin A1c targets for elderly people with comorbidities. Accordingly, less than 5 years of life expectancy is an acceptable threshold for identifying older patients who are unlikely to benefit from intensive glycemic control [51].

Creating a patient-centered protocol in aggreement with the 'Guidelines for Improving the Care of the Older Persons With Diabetes Mellitus' entails the following key points [54]: first, estimation of the patient's approximate life expectancy; second, decision on intensive glycemic targets for older adults with a life expectancy of longer than 8 years (sic) and a low risk of hypoglycemia; third, the choice of symptom management and strategies to improve quality of life for frail older adults, those with a high burden of illness, difficulty adhering to therapy, or a short life expectancy.

IV. Treatment of Hyperglycemia in the Acute Geriatric Ward

It has been proposed that each hospital designate a multidisciplinary team for improving glucose control, being in charge to establish pertinent glycemic goals, treatment algorithms, the system for documentation of blood glucose, nutrition and treatment data, and supervise the results of the intervention [55].

The Glycemic Goal

An easily accepted strategy and considered to be safe is a stepwise approach, starting with an initial blood glucose goal of less than 200 mg/dL, and then progressively stepping down the goal as experience is gained. The initial blood glucose goal of less than 200 mg/dL is realistic, less demanding to the nursing staff, entails smaller risks to patients, and is more easily accepted in practice [55]. Such goal is also scientifically acceptable: renal threshold for glucosuria is around 180 mg/dL [56] and improvement in granulocyte adherence was observed when glucose levels decreased to 198 mg/dL [31]. Clinical data showed non-inferiority by applying a protocol of glycemic control aiming to blood glucose of less than 180 mg/dL in comparison to close-to-normal glycemic management [46,47]. This goal is in agreement with the principle to avoid persistent hyperglycemia >200 mg/dL [57].

In our geriatric ward, glycemic targets were individualized in agreement with the 'Guidelines for Improving the Care of the Older Persons with Diabetes Mellitus' [52]. For older adults with a life expectancy of longer than 8 years and a low risk of hypoglycemia we set a blood glucose goal <200 mg/dL. The <200 mg/dL blood glucose goal is realistic and was met in our ward in 72 % of blood glucose measurements. A blood glucose goal <250 mg/dL was set for frail older adults and those with a high burden of illness.

An Algorithm

The protocol proposed by Inzucchi and published in the New England Journal of Medicine in 2006 [45] has been adopted, with certain modifications, to be used in our geriatric ward. A detailed description of this protocol is beyond the scope of the present discussion. The following points deserve emphasis:

1. Patients who were on oral hypoglycemic medications may continue their previous hypoglycemic medications when glycemia is fairly controlled, no contraindications preclude their use, and the patients are expected to eat regularly during the hospitalization. There may be a temporary contraindication to use of metformin. If gycemia is poorly controlled, the oral agents should be discontinued and insulin treatment started; insulin treatment is based on the combination of basal, prandial and correction insulin.

2. Insulin treatment should replicate the normal insulin secretion as closely as possible [39,45,58,59]. Therefore, requirements of basal insulin should be supplied as well as requirements of prandial insulin. Correction insulin should be added when the blood glucose exceeds 150 mg/dL; correction insulin is usually supplemented to mealtime insulin. The traditional treatment with regular insulin by sliding scale as the sole form of glucose control should be abandoned. In our ward, the combination of a basal insulin (NPH every 12 hours or glargine every 24 hours) with rapid-acting insulin is most commonly prescribed. Insulin glargine is associated with a lower risk of hypoglycemia as compared to neutral protamine Hagedorn insulin and premixed insulin formulations, beside improvements in glycemic control [50, 60-62]. Therefore, insulin glargine could turn out to be the treatment of choice for elderly patients [62,63], inclusive patients on continuous enteric tube feeding [64].
3. Patients who where on insulin treatment prior to admission and expected to eat regularly during the hospitalization will continue the regimen used before hospitalization if the glucose level on admission is acceptable. If the glucose level on admission is >200 mg/dL, the insulin dose will be increased.
4. Modest dose reductions are made when a reduction in caloric intake is anticipated.
5. In patients whose dietary intake is uncertain, dosing of prandial insulin is problematic. In this situation a rapid-acting insulin analogue (lispro, aspart) is preferred, to be administered immediately after the meal on the basis of the serving that the patient has actually consumed.
6. For insulin-treated patients who are not eating, the basal insulin needs (twice daily NPH or once daily glargine), are adjusted according to the morning fasting blood glucose level. Regular insulin is added every 6 hours as necessary.
7. Intravenous infusion of insulin is prescribed if glucose levels >300 mg/dL persist longer than 24 – 48 hours and are not controlled by increasing the dose of subcutaneous insulin. Intravenous insulin works rapidly, and the dose can be titrated more precisely than the dose of subcutaneous injected insulin. Many hospitals restrict use of intravenous insulin infusion to critical care units based on the erroneous belief that intravenous insulin infusion is more risky than subcutaneously administered insulin. The onset of action of intravenous insulin is within a few minutes with a duration of action of only about an hour. In contrast subcutaneous insulin has a much slower onset of action, its effect can be prolonged and is unpredictable in acutely ill patients. There are numerous reports in the literature of prolonged and severe hypoglycemia with overdose of subcutaneous insulin, including the rapid-acting analogues [55]. In reality intravenous insulin with appropriate monitoring is safer than subcutaneous insulin.
8. Patients receiving continuous enteral tube feeding are managed mainly with basal insulin; correction doses of regular insulin are added as needed every 6 hours. If feeding is interrupted, an amount of dextrose similar to that being used enterally is administered intravenously in order to prevent hypoglycemia.

Documentation of Blood Glucose and Insulin Infusion Data

Graphic representation of blood glucose and insulin data simplifies the recognition of glucose trends and may contribute to judicious therapeutic decisions. Ideally this data may be managed in a computerized system at the bedside. It is usually recommended to check capillary blood glucose every hour until it is in the goal range for 4 hours [55]. This is not willingly accepted by the nursing staff in the geriatric ward and is reserved in our unit for high risk patients.

Nutritional needs are changing during catabolic illness. Monitoring the parameters of nutrition and glycemic status is essential, so that both nutritional needs are met and glycemic control is maintained. Catabolic illness can also alter the fluid balance. The length of time the patient will be unable to eat should be considered, together with the degree of recent weight loss and the presence of excess fluid that is often present in severely ill patients. All these factors determine the nutrition needs [65]. Enteral feeding has several advantages over parenteral feeding, including lower costs, avoidance of catheter-related complications, the trophic effect of food on gastrointestinal cells, and stimulation of the incretin pathway [58]. Current enteral nutrition formulas are generally high in carbohydrate (45–92% of calories) and low in fat and dietary fiber [66]. Enteral formulas contain 7–16% of total calories from protein and 25–40% from fat. There are a variety of different protein sources in these enteral feedings, and there are no contraindications for use of any of these in people with diabetes. For most institutionalized patients, it is recommended that protein intake should be 1.2–1.5 g/kg/day [67]. There is controversy as to how much of the alimentary fat should be from n-3 compared with n-6 fatty acids. In general, products that are lower in carbohydrate and higher in dietary fiber and fat have less of an impact on diabetes control [68].

Patients receiving continuous enteral tube feeding can be managed with once daily insulin glargine, starting with a small basal dose; correction-dose insulin is added as needed while the glargine dose is being titrated [58]. For intermittent enteral feeding, NPH insulin with adding a small dose of regular insulin is recommended. The NPH insulin provides basal insulin coverage, while the regular insulin is administered before each tube feeding to control postprandial glucose levels. Doses should be calculated based on capillary glucose testing before and 2 hours after each enteral feeding [58].

V. Hypoglycemia

The definition proposed by Whipple is still the most useful and identifies pathologic hypoglycemia as a triad of low plasma glucose, hypoglycemic symptoms, and resolution of symptoms with correction of the blood glucose [69]. The biochemical criterion alone is not sufficient for the diagnosis of hypoglycemia because plasma glucose values below the normal may reflect laboratory error or artifactual hypoglycemia from glycolysis within the collected sample (due to erythrocytosis or leukocytosis). In addition, the level of glucose to define hypoglycemia is a source of controversy; values <40, 50 or 60 mg/dL have been defined as hypoglycemic for different populations, clinical purposes, or circumstances [70]. It is noteworthy that glucose levels measured by fingerprick meters are about 10%-15% lower

than venous plasma levels. Therefore, use of fingerprick glucose meters for diagnosis of hypoglycemia may be misleading. Thus, a fingerprick meter glucose reading of 39 mg/dL could correspond to laboratory serum glucose 53 mg/dL [71]. Many other factors can affect point-of-care blood glucose measurements; such are the amount of blood on the glucometer strip, the hematocrit value, peripheral hypoperfusion states (shock, vasoconstriction), delay of sample processing, severe lipemia, certain medications (levodopa, acetaminophen), high unconjugated bilirubin)[72].

Symptoms caused by a sudden drop in blood glucose reflect the effects of hypoglycemia on the nervous system, including increased autonomic nervous system activity (anxiety, tremulousness, palpitation, sweating, nausea, hunger) and neuroglycopenic impairment of the central nervous system (weakness, fatigue, confusion, seizures, focal neurological deficit, and coma). 'Hypoglycemic symptoms' are nonspecific and unreliable to diagnose hypoglycemia. Conditions that present with similar symptoms need to be excluded by assessing blood glucose values. 'Hypoglycemic symptoms' may be absent or may not be perceived as such [73]. Only 22% of residents of a long-term care facility who suffered from an episode of infection-related hypoglycemia showed clinical signs indicating hypoglycemia [11].

Hypoglycemia in the diabetic patient is most often caused by insulin or oral hypoglycemic medications. More intensive glucose control with lower average glucose levels significantly increases the risk of hypoglycemia, sometimes severe. The risk of hypoglycemia becomes greater as insulin deficiency progresses and patients with type 2 diabetes also have developed impaired glucagon and epinephrine release in response to hypoglycemia [74]. Beside hypoglycemic medications causes of hypoglycemia include critical illnesses (hepatic, cardiac, or renal failure), sepsis, inanition and endocrine deficiencies (cortisol, growth hormone, or both).

Illustrative is the case of a diabetic patient previously attended by us, whose daily insulin requirement was 56 units until he developed an episode of acute post-streptococcal glomerulonephritis. Acute reversible renal failure ensued. At this stage the insulin requirement diminished to 8 units/day. The insulin requirement returned to its previous level after the patient recovered from acute renal failure [75]. In other patients, sepsis, adrenal insufficiency or acute hepatic failure caused the rapid decline in insulin requirement leading to hypoglycemia.

Most episodes of asymptomatic hypoglycemia (detected by serum glucose measurements) as well as mild to moderate symptomatic hypoglycemia are effectively treated by ingestion of glucose tablets or carbohydrate in the form of juices, soft drinks, milk, crackers, candy, or a meal. However, the instantaneously corrected hypoglycemia by oral glucose intake can recur within less than 2 hours. Therefore, shortly after the plasma glucose level has raised the patient should ingest a more substantial mixed snack. Parenteral treatment is necessary when a hypoglycemic patient is unable to take carbohydrate orally. Intravenous glucose, 25 g initially (50cc of the 50% solution), is the standard intravenous therapy followed by lasting infusion of glucose; food should be provided as soon as the patient is able to take it safely. Glucagon is an effective emergency treatment for hypoglycemia where intravenous treatment with glucose is not available. Glucagon can be injected subcutaneously or intramuscularly by a spouse or family member. The standard dose of 1 mg can cause substantial but transient hyperglycemia [76].

In conclusion, hyperglycemia whether diabetic or stress-induced, is associated with increased risk of morbidity and mortality in the setting of an acute illness and should be quickly and safely controlled. The glycemic goals are individualized according the patient's geriatric syndromes, associated medical conditions and the patients' health care goals. In the acute geriatric ward, we decided on a blood glucose goal of less than 200 mg/dL for older adults with a life expectancy of longer than 8 years and a low risk of hypoglycemia. A looser blood glucose control may be acceptable for frail older adults or those with a high burden of illness. To safely achieve these goals a dedicated team should be assigned, including internists, endocrinologists, nurses, and nutritionists.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter V

Postprandial Syndrome in the Elderly

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Important diagnostic hints can be found in the circumstances of a symptom's appearance, the association with specific triggers, and the time elapsed between advent of the eliciting factor and onset of the symptom. These three features may be pertinent to the assessment of symptoms which return stereotypically after meals in a variety of disorders: peptic ulcer pain [1], dyspeptic syndromes [2], postcholecystectomy syndrome [3], dumping syndrome [4], gastroparesis [5], chronic intestinal angina [6], partial small bowel obstruction [7], reactive hypoglycemia [8] and postprandial hypotension [9]. When a patient's postprandial symptoms match one of the typical patterns, the diagnostic alternatives are few and the work-up can be targeted to a small number of entities (Figure 1). However, a patient's postprandial symptoms may be vague and not matching any typical pattern. This latter situation is more often met in elderly patients. Indeed, interviewing elderly patients may require great perseverance yet may be unproductive, especially in subjects with poor memory, confused or hard of hearing [10]. In such situation it may be advisable to expand the diagnostic work-up, seeking to face the whole spectrum of postprandial syndrome.

Postprandial pain, discomfort, palpitations, dizziness or syncope may be the leading postprandial symptom. In searching the Medline data base, we could not find clinical trials or expert opinion to guide the management of elderly patients with recurrent postprandial symptoms. Based on the review of the literature and the author's personal experience, a diagnostic algorithm for evaluation of recurrent postprandial symptoms is proposed. This algorithm is particular aimed for elderly patients.

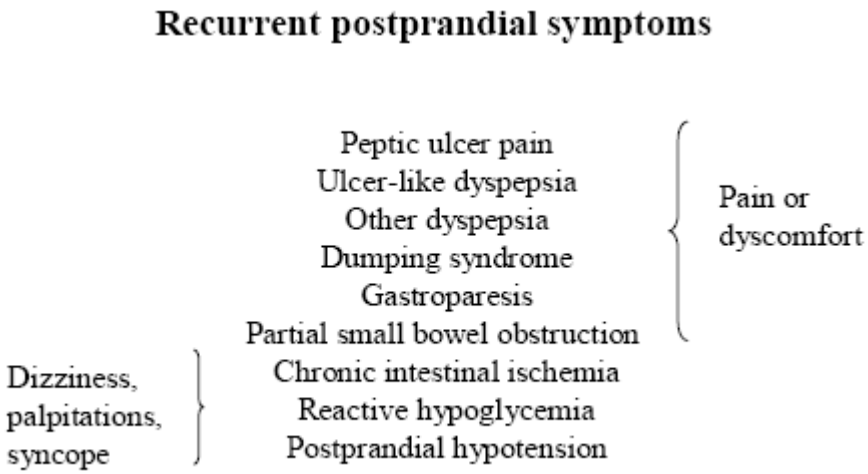

Figure 1. Proposed classification of postprandial syndrome.

Peptic Ulcer Disease in the Elderly

The incidence of gastric and duodenal ulcers and their bleeding complications is increasing in old-aged populations worldwide [11-13]. Among etiologic factors associated with peptic ulcer disease in the elderly, helicobacter pylori infection and intake of non-steroidal anti-inflammatory drugs are the most frequently encountered. Helicobacter pylori is present in 53-73% of elderly patients with peptic ulcer disease. Forty per cent of gastric ulcers and 25% of duodenal ulcers in elderly patients are associated with the use of non-steroidal anti-inflammatory drugs or aspirin [14]. Typical epigastric pain occurred in just 35 % of patients older than 65 years vs. 91% of younger ulcer patients; atypical pain location was described in 39% of elderly vs. 15% of younger ulcer patients [1]. Nausea and gastroesophageal reflux were significant associates of peptic ulcer disease, but epigastric pain or discomfort were not [15]. Endoscopy is the preferred modality for the diagnosis of peptic ulcer because of its high accuracy and the ability to take biopsies of suspicious looking ulcers.

Dyspepsia

Diagnosis of functional dyspepsia requires presence of one ore several of the symptoms - bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning; onset of symptoms at least six months before and symptoms present for the last three months; no evidence of structural disease likely to explain the symptoms (including on evaluation by upper endoscopy) [2]. Dyspeptic symptoms are very common in the elderly, but the vast majority of patients have modest symptoms and rarely seek medical advice. Symptom patterns alone do not discriminate organic from functional dyspepsia [16].

It is largely agreed that robust and fit elderly patients having recurrent postprandial abdominal pain, dyspeptic symptoms or nausea should undergo early endoscopy, in view of the higher proportion of patients with organic disease and the likelihood of malignancy [17]. It is also recommended that patients with significant weight loss, gross or occult bleeding, dysphagia, severe vomiting, or profound early satiety also be referred for early endoscopy [17]. Patients with dyspeptic symptoms who are not candidates for early endoscopy may be empirically treated with antisecretory or prokinetic agents. Antisecretory agents are preferred as they are better tolerated and effective in the treatment of gastro-esophageal reflux disease as well as peptic ulcer disease. Proton pump inhibitors are the first line agents [15,16]. Testing dyspeptics for helicobacter pylori and treating those who are infected has become popular; this strategy is also effective in treating peptic ulcer disease and is cost saving [17,18].

Dumping Syndrome

Dumping syndrome is a group of signs and symptoms that develop most often in subjects who have had surgery to remove all or part of their stomach. Dumping syndrome may also develop in obese subjects whom much of their stomach has been surgically bypassed to promote weight loss. The symptoms, mainly nausea, vomiting, epigastric fullness, cramping, diarrhea, dizziness, flushing, start within one hour after eating. A detailed clinical history and evidence of prior gastric surgery usually makes the diagnosis of dumping syndrome. Scintigraphic imaging documents rapid gastric emptying and may be useful in rare instances when patients have dumping syndrome in the absence of prior gastric surgery [19].

Postcholecystectomy Syndrome

Postcholecystectomy syndrome refers to the occurrence of abdominal symptoms after cholecystectomy. The term is inaccurate because it comprises a spectrum of biliary and nonbiliary disorders that are rarely related to the operation itself. The most common postoperative symptoms noted are dyspepsia, flatulence, and bloating, which usually antedate the cholecystectomy. Other patients have persistence of right upper quadrant or epigastric pain. Persistence of pain after surgery or early recurrence of pain shows that the abdominal symptoms were not caused by gallbladder pathology. The differential diagnosis of symptoms after cholecystectomy includes choledocholythiasis, peptic ulcer disease, irritable bowel syndrome and psychiatric disorders [3,20].

Gastroparesis

Gastroparesis is manifested by nausea, early satiety, postprandial epigastric pain and vomiting. The main causes of gastroparesis are diabetes mellitus, scleroderma, vagotomy, chronic intestinal pseudo-obstruction, neurologic disorders, gastric resection, or viral

illnesses; sometimes no specific cause can be found [5]. Scintigraphic techniques have become the mainstay of the assessment of gastric emptying for the diagnosis of gastroparesis [19].

Partial Small Bowel Obstruction

Partial small bowel obstruction may be suspected if postprandial pain begins 3 to 5 hours after the meals, is cramping in nature, extends diffusely over the abdomen, and progressively increases in severity over several weeks or months. Abdominal distention and inability to pass flatus are often present. Hints to the cause of partial small bowel obstruction may be found in surgical scars (indicating adhesions as the underlying cause), the finding of an incarcerated hernia on examination of hernial orifices, rectal examination demonstrating intraluminal masses or occult blood (which suggest possible malignancy, intussusception, or infarction [7].

Chronic Mesenteric Ischemia

Chronic mesenteric ischemia (also called intestinal angina) refers to intestinal hypoperfusion, which usually develops in patients with mesenteric atherosclerotic disease [21]. Abdominal pain occurs soon after eating and is caused by ischemia in the small intestine, as blood is diverted from the intestine to the stomach when food enters the stomach, in meeting the increased demand for gastric blood flow [21]. This 'steel phenomenon' explains why pain of intestinal ischemia occurs early after eating. The cardinal clinical feature of chronic mesenteric ischemia is abdominal cramping discomfort that usually occurs within 30 minutes after eating, gradually increases in intensity, then slowly resolves over 1 to 3 hours. The association of pain with meals leads to fear of eating with resultant weight loss. Nausea, bloating, episodic diarrhea, and malabsorption or constipation may occur. The symptoms progressively increase in severity over weeks to months.

The diagnosis of chronic mesenteric ischemia is difficult because of the vague nature of the complaints and the lack of a specific diagnostic test. Angiography is expected to show occlusion of two or more splanchnic arteries to be consistent with the diagnosis; however, occlusion even of all three vessels do not establish the diagnosis of chronic mesenteric ischemia, because they may be present in patients who do not suffer of intestinal angina [22]. On duplex ultrasonography, a peak systolic velocity >275 cm/s of the flow in the superior mesenteric artery identifies >70% stenosis; the velocity threshold >275 cm/s has sensitivity of 92%, positive predictive value 80% and negative predictive value 99% for chronic mesenteric ischemia [23].

Diagnosing chronic mesenteric ischemia is based on clinical symptoms along with radiological demonstration of an occlusive process of the splanchnic vessels and, to a great measure, the exclusion of other gastrointestinal disorders [5,24]. Successful treatment is possible by percutaneous or surgical revascularization [25].

Postprandial Hypotension

There is no generally accepted definition of postprandial hypotension. In analogy to orthostatic hypotension, postprandial hypotension is commonly diagnosed when the systolic blood pressure diminishes by 20 mm Hg or more within 2 hours of eating a meal [9]. The diagnosis of postprandial hypotension is acceptable also with less decrease of blood pressure, when the absolute level of systolic blood pressure after a meal become decreases to less than 90 mm Hg while the systolic blood pressure before the meal was greater than 100 mm Hg. Important clinically is the fall of systolic blood pressure below the threshold for cerebral autoregulation; at this point a meal-related decrease in blood pressure may become symptomatic [9]. Symptoms of postprandial hypotension include dizziness, weakness, lightheadedness, syncope, transient ischemic attacks, nausea, disturbed speech, and angina pectoris. Postprandial hypotension is an independent predictor of all-cause mortality [26]. It is important to recognize that patients are often unaware of postprandial hypotension unless their blood pressure is measured before and after eating.

Investigations of elderly people living in nursing homes have shown that nearly all experience some postprandial decrease in blood pressure. In 24% to 36% of these patients, systolic blood pressure decreased more than 20 mm Hg within 75 minutes of eating a meal [27, 28]. Postprandial hypotension can also unmask orthostatic hypotension in patients who at other times cope adequately with orthostatic stress. Profound postprandial hypotension has been observed in patients with autonomic failure, in patients with peripheral neuropathy caused by diabetes mellitus or other disorders, as well as in Parkinson disease [9]. Postprandial hypotension occurred with similar frequency in orally fed, in nasogastric tube-fed, and gastrostomy-fed elderly people [29]. Because the high prevalence of symptomatic postprandial hypotension and orthostatic hypotension in the elderly, it was proposed that blood pressure measurements for diagnosing hypotensive syndromes should be an integral part of comprehensive geriatric assessment: we should consider not only orthostatic, but also postprandial blood pressure changes [30].

Automated ambulatory blood pressure monitoring is a simple and inexpensive way in which we can improve the diagnosis of postprandial hypotension. Yet, diagnosing postprandial hypotension is not as undemanding as it might appear, since the time to nadir blood pressure may vary, the magnitude in blood pressure drop after meals may differ in relation with the meal's composition [31, 32], with the patient's position seated or supine, and there may be day to day [33] as well as seasonal variability of postprandial hypotension (Figure 2). In nursing home residents, the systolic blood pressure nadir occurred as early as 15 minutes after the meal in 13% to 17% of the patients and as late as 75 minutes after the meal in 11% to 13% of the patients [27, 28]. A protocol for investigating postprandial hypotension [34] applicable both in research and practice is shown in Figure 3.

Strategies for the treatment of postprandial hypotension are directed at meal composition (particularly carbohydrate type and content), increasing prandial gastric distension, slowing gastric emptying, and slowing absorption of cargohydrates in the small intestinal [9,35]. A detailed description of the treatment is beyond the scope of this article. Recently, the alpha-glucosidase inhibitors acarbose and voglibose were reported to be effective for the treatment of postprandial hypotension, probably due to delayed glucose absorption by inhibiting

conversion of carbohydrates to monosaccharide [36] and by reduction of splanchnic blood pooling by inhibiting the release of vasodilative gastroenteric peptides, such as neurotensin [35]. Acarbose attenuated the postprandial fall in systolic blood pressure by average 17 mm Hg [37] and voglibose by average 20 mm Hg [34]. Voglibose was associated with fewer gastrointestinal side effects than acarbose.

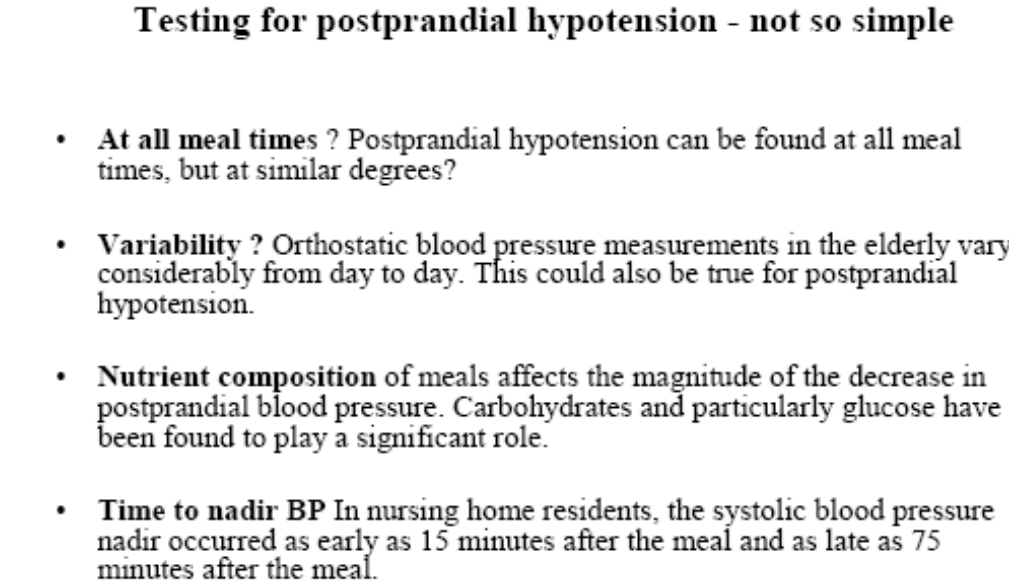

Figure 2. Sources of possible errors in evaluating patients for suspected postprandial hypotension.

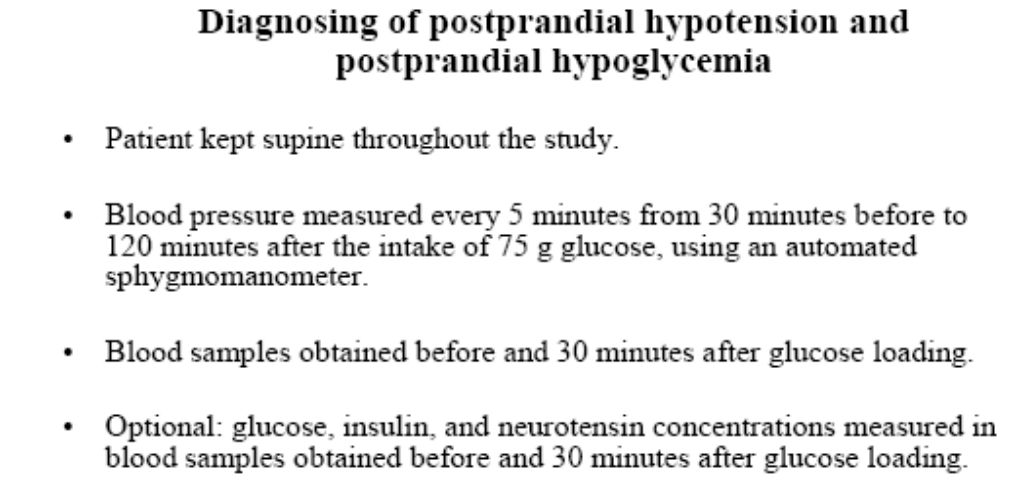

Figure 3. Proposed protocol for the diagnosis of postprandial hypotension and postprandial hypoglycemia.

Postprandial Hypoglycemia

Postprandial (reactive) hypoglycemia occurs after meals, typically within 4 hours after food ingestion. Postprandial hypoglycemia can arise in individuals who have undergone gastric surgery that results in rapid movement of ingested food into the small intestine [38]. Hypoglycemia is thought to be the late consequence of rapid postprandial increment in plasma glucose, resulting in marked hyperinsulinemia and subsequent hypoglycemia, that manifests 1.5 to 3.0 hours after food ingestion. Enhanced secretion of incretins (these are gastrointestinal peptide hormones released from intestinal endocrine cells after exposure to food) may also be involved in this process [39].

The mere existence of idiopathic postprandial hypoglycemia continues to be subject to controversy [40]. Adepts of the concept maintain that postprandial hypoglycemia can be diagnosed if sympathetic and neuroglycopenic symptoms develop after a meal, concurrently with blood sugar <60 mg/dL, and relief of those symptoms occurs as the plasma glucose concentration rises (Whipple's triad) [8]. Symptoms caused by a sudden drop in blood glucose reflect the effects of hypoglycemia on the nervous system: increased autonomic nervous system outflow (such as anxiety, tremulousness, palpitation, sweating, nausea, hunger) and neuroglycopenic compromise of the central nervous system (such as weakness, fatigue, confusion, seizures, focal neurologic deficit, and coma).

Others argue that there is little evidence to support the existence of postprandial hypoglycemia as a nosologic entity [40-45]. Indeed, symptoms of 'postprandial hypoglycemia' are not specific, glucose levels have rarely been measured when postprandial symptoms developed spontaneously, and blood glucose concentrations measured after oral glucose administration correlate weakly with 'hypoglycemic symptoms'. In one series of patients in whom blood glucose was measured during suspected 'hypoglycemic events', only 5% of 132 episodes were associated with blood glucose levels of 50 mg/dL or less [42]. In another study, merely 16 of 118 patients suspected of having postprandial hypoglycemia had low plasma glucose concentration and typical symptoms after an oral glucose load; just 5 of those 16 patients had similar symptoms after their regular meals [43]. Administration of an α-glucosidase inhibitor which competitively inhibit pancreatic amylase, thus delaying gastrointestinal absorption of carbohydrates, is a conceptually attractive treatment for these patients although controlled trials indicating its efficacy are lacking.

Proposed Diagnostic Approach

The approach to patients with recurrent postprandial symptoms depends on the patient's health care goals and preferences, implementation of ways that lead to efficient treatment and minimizing unnecessary costs. Elderly adults exhibit heterogeneous health status ranging from robust to frail [46]. The patient's general health status and goals of care are important when prioritizing clinical recommendations for elderly adults [46,47]. For some patients, maintaining functional independence and avoiding the financial, physical, and psychological burden of health care takes precedence over intense medical management and long-term preventive strategies. Others prefer an aggressive approach to medical management and risk

reduction. Physicians caring for elderly adults may turn to clinical care guidelines as a source that summarizes the best evidence for evaluation and management of conditions affecting their patients. However, most guidelines for conditions affecting elderly adults are disease-focused and do not provide guidance for prioritizing multiple medical conditions and geriatric syndromes, that are common in elderly adults [47].

The 'Guidelines for Improving the Care of Older Persons with Diabetes Mellitus' address this complexity [47] and also could serve as a model and reference for the judicious evaluation and treatment of geriatric patients presenting other medical problems, for example recurrent postprandial symptoms. As a general rule, patients with unusually good health and function may be candidates for comprehensive evaluation; these patient's health care goals and preferences for treatment should be discussed and the patient helped to prioritize treatment options. On the other hand, frail older adults or those with a short life expectancy are not candidates for invasive testing [46,47].

After having clarified the goals and limitations of the diagnostic procedures as well as therapy in the individual patient), the ways that lead to faster treatment while minimizing unnecessary costs are asked for, in conformity with Sutton's law (*'go where the money is'*) [48]. In facing robust and fit elderly patients, the diagnostic work-up is symptom-oriented and carried out according to the general clinical guidelines [24,49,50]; elderly patients having recurrent postprandial abdominal pain, dyspeptic symptoms or nausea should undergo early endoscopy, in view of the higher proportion of patients with organic disease and the likelihood of malignancy; chronic mesenteric ischemia should be considered next. Patients with postpradial weakness, dizziness or syncope should be evaluated for suspected postprandial hypotension, while reactive hypoglycemia is an unlikely possibility, except for patients with a history of gastric surgery.

Frail elderly adults, those with difficulty adhering to therapy, or a short life expectancy are not candidates for invasive testing; they more likely would benefit from symptom management with a proton pump inhibitor or prokinetic agents. Just as in fit elderly subjects, the possibility of postprandial hypotension should be tested in frail elderly patients, because of the high prevalence of postprandial hypotension and the possibility of effective treatment. The possibility of postprandial hypotension is a concern also in patients having malaise or profound sleepiness after a meal.

We could not find in the literature prospective clinical trials or expert opinion to guide the management of patients with recurrent postprandial symptoms. An algorithm is proposed, centered on the particular health problems of elderly patients (Figure 4).

Conclusions

The approach proposed herein to the diagnosis and treatment of recurrent postprandial symptoms in the elderly is supported by data from the literature and the authors experience and preferences. No randomized prospective studies are available on these issues to serve as guidelines. Further studies are needed to improve the level of evidence that is available for developing recommendations.

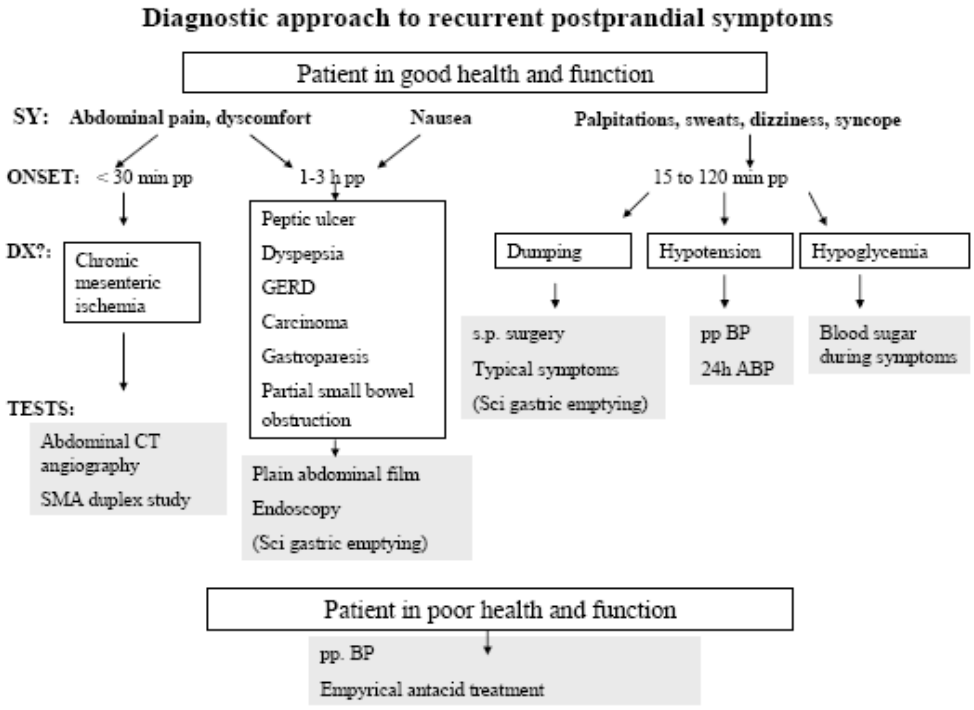

Figure 4. Evaluation of postprandial syndromes.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter VI

Management of Sepsis

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Sepsis is the term used to describe the body's systemic responses to infection. A consensus committee of American experts in 1992 defined sepsis as a systemic inflammatory response syndrome due to presumed or confirmed infection. Nonspecific symptoms such as tachycardia, leukocytosis and fever may be inflammatory in nature; when occurring in concert they constitute the 'systemic inflammatory response syndrome' (SIRS). SIRS occurring in a patient with proven or suspected infection is called 'sepsis' [1]. A review of the National Hospital Discharge Survey (U.S.A) data found that the incidence of sepsis increased by almost fourfold during the interval from 1979 to 2000, to 240 cases per 100,000 population per year [2].

Sepsis causes considerable morbidity, cost, health care utilization and mortality. Hospital mortality for sepsis patients ranges from 18% to 30%, depending on the series. While the mortality rate has decreased over the past 20 years, an increase in the number of sepsis cases has resulted in a tripling of the number of sepsis-related deaths [3]. There is a growing awareness of the need for an organized approach to caring for patients affected by sepsis. An early diagnosis of sepsis, prior to the onset of clinical decline, allows for prompt antibiotic administration and goal-directed resuscitation. The time to initiate therapy is thought to be crucial and the major determining factor for surviving sepsis [4,5], similar to the critical time-limit for early interventions in management of acute myocardial infarction and ischemic stroke.

Elderly patients are at increased risk to develop sepsis. In fact, age greater than 65 years is associated with a 13.1 times increased risk to contract sepsis vs age less than 65 years [6]. Hence, appropriate care for sepsis is a major issue in the acute geriatric ward. The spread of multidrug-resistant Gram-negative and Gram-positive organisms in geriatric wards implies the need to delay development of antibiotic resistance. To this aim, choosing the right drugs

and dosing regimens, monitoring antibiotics use and avoidance of their overuse are important measures [7,8].

This chapter will center on the diagnosis and management of sepsis in the geriatric ward and on infection containment. Preference will be given to problems faced more recently by the authors.

I. Basics

For sepsis to occur, a large bacterial inoculum must break the host's defenses [3]. Nearly all bacteria are capable of causing sepsis, at least in immuno-compromised patients. Many infections arise from the patient's own bacterial flora. *Staphylococcus epidermidis* normally colonizes the human skin, but when it invades the bloodstream, it can cause septicemia, endocarditis, or infections of prosthetic joints. *Staphylococcus aureus* colonizes the skin and mucosal surfaces in the nose in 30% of the population. When it extends to other sites, staphylococcus aureus can cause skin abscesses, arthritis, endocarditis and necrotizing pneumonia. When bacteria from the oral cavity are aspirated to the lungs pneumonia can evolve. *Escherichia coli,* which is a normal inhabitant of the gut, may enter the blood stream and cause a variety of infections. Bacteria are often considered the sole causative agents of sepsis, but any microorganism can cause sepsis, including fungi, parasites, and viruses [3].

The interaction of microbiological products with a susceptible host induces a cascade of immunomodulatory mediators which are largely responsible for the clinical symptoms and signs of sepsis. So, sepsis is the systemic inflammatory response syndrome secondary to an infection, a dynamic process caused by imbalance in the 'inflammatory network' [9]. The major pathways involved in sepsis include the innate immune response, inflammatory cascades, procoagulant and antifibrinolytic pathways, alterations in cellular metabolism and signaling, and an acquired immune dysfunction [3]. A detailed description of the mechanisms operative in sepsis is beyond the aim of the present discussion, and can be found in recently published reviews [10-12].

Aging is accompanied by the decline in cell-mediated and humoral immune functions, contributing to the enhanced susceptibility to infection. In the elderly, cytokine and chemokine signaling networks are altered with a predominant type 2 cytokine response over type 1 cytokine response; induction of proinflammatory cytokines after septic stimuli is inadequately controlled by anti-inflammatory mechanisms. The pathophysiologic cascades operative in sepsis, when insufficiently countered by homeostatic defenses, may render elderly patients at increased risk for major organ dysfunction, shock and death [13].

The clinical manifestations of sepsis comprise a spectrum that ranges from minor signs and symptoms to organ dysfunction and shock [14]. At first presentation, symptoms of sepsis may be atypical, sometimes making early diagnosis difficult. Altered mental status may be the sole presenting sign of sepsis in elderly subjects. Atypical presentations, such as the absence of fever, tachycardia or leukocytosis, are more prevalent in the older age groups. This is illustrated in a notable study comparing the manifestations of bloodstream infections at different ages [15]. The oldest patients (≥85 years old) and elderly patients (65-84 years old) had more often atypical manifestations, more frequent organ failure and a worse

prognosis than younger adults (18-64 years old). Elderly patients had significantly less tachycardia, more often acute respiratory failure and renal failure. Sepsis in the oldest old patients occurred more without fever and leukocytosis, while the oldest old developed more often respiratory failure, acute renal failure, septic shock, and altered mental status. Urinary tract infections were the main source of blood stream infections for both the elderly and oldest old. The oldest old had significantly more pneumonia than the elderly or younger adults. The oldest old patients had a significantly higher frequency of polymicrobial bacteremia. The three most common bacteria across age classes were Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus [15]. In another study, oldest old bacteremic patients had higher percentage of infections with Gram-negative organisms and Staphylococcus aureus, empirical antibiotic treatment was more often inappropriate, and bacteremia-related mortality was greater [16].

A favorable outcome of sepsis depends on early and aggressive treatment. Implementation of a comprehensive sepsis treatment protocol is feasible and is associated with changes in therapies such as administration of antibiotics, delivery of intravenous fluids, and use of vasopressor in the first 6 hours after onset of symptoms [4,5].

II. Sepsis Management Routine

A routine should be followed to optimize the management of sepsis: blood and urine cultures should be taken; imaging studies be performed promptly to confirm the potential source of infection; empirical treatment with a broad-spectrum antibiotic be immediately started; subtle signs of organ hypoperfusion should be pursued and corrected; after results of microbiology cultures are available, the antibiotic coverage needs to be narrowed as appropriate [17,18].

Collection of Specimens

Often physicians are unfamiliar with guidelines for specimen collection and transport; emphasis on technical details on this subject is desirable [19]. Collection of specimens for culture of specific microorganisms should start before the administration of chemotherapeutic agents so that the recovery of microorganisms will not be compromised. Careful collection may prevent the specimen's contamination with normal flora. For instance, blood cultures should always be taken with gloves, the venipuncture site should be prepared either with povidone-iodine, or 70% alcohol; both are applied in a circular fashion to the puncture site. Then, 10 to 20 mL of blood are drawn and injected into the blood culture bottles. These are to be transported ASAP to the microbiology laboratory to start incubation. Upon suspicion of infection of a central venous catheter, the catheter should be removed aseptically and a 4 cm segment or longer cut from the tip should be placed in a sterile container. For urine cultures, a midstream specimen should be properly collected. Straight catheter collection provides proper specimen without or less contamination. Urine cultures may either be transported

promptly to the laboratory or kept refrigerated. In distinction from intravenous catheters, urinary catheters are not acceptable for culture [19].

Antibiotic Treatment for Sepsis

The choice of empiric antibiotics depends on the clinical syndrome, underlying disease, susceptibility patterns of pathogens in the community and in the hospital, susceptibility of pathogens that previously have been shown to colonize or infect the patient, as well as the patient's drug intolerances [18]. Because patients with severe sepsis or septic shock have little margin for error in the choice of therapy, the initial selection of antimicrobial therapy should be wide-ranging to cover all likely pathogens. Failure to initiate appropriate therapy correlates with increased morbidity and mortality [20-22].

Empirical antimicrobial therapy depends upon localizing the site of infection to a particular organ, which indicates the probable pathogenic flora in the septic process and is the basis for the selection of appropriate empiric antimicrobial therapy [23]. The most common conditions associated with sepsis are urinary infections, pulmonaty, hepatobiliary, colon and pelvic infections, central venous catheter infections and intravascular infections. The possibility of nosocomial infection with multidrug resistant pathogens is a major consideration [24]. Recently used antibiotics should generally be avoided. *Monotherapy* is preferred to polypharmacy, which increases costs, potential for side effects and for drug–drug interactions. Patients should receive a full loading dose of each antimicrobial, but in taking account that patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. *Combination therapy* is recommended for patients with known or suspected pseudomonas or enterococcus as a cause of severe sepsis; also combination empirical therapy is recommended for neutropenic patients with severe sepsis. When used empirically in patients with severe sepsis, combination therapy should not be administered for longer than 3–5 days [23].

When results of microbiology become available, antibiotic therapy is reassessed to narrow the coverage [18]. It may become apparent that none of the empirical drugs that have been administered offer optimal therapy; there may be another drug proven to produce superior clinical outcome that should therefore replace empirical agents. Narrowing the spectrum of antibiotic coverage and reducing the duration of antibiotic therapy reduces the likelihood that the patient will develop superinfection with pathogenic or resistant organisms, such as Candida species, Clostridium difficile, or vancomycin-resistant Enterococcus faecium. However, the wish for minimizing superinfections should not take priority over the need to give the patient an adequate time of treatment to cure the infection which caused the severe sepsis or septic shock [18]. De-escalation is not necessary if initial monotherapy was suitable [23]. Drug serum concentration monitoring can be useful for those drugs that can be measured promptly [18].

Local unit specific antimicrobial sensitivity data are important in selecting empiric therapy and institutional practices for management of sepsis have been proposed. Illustrative is the Winthrop-University Hospital protocol [23], based on prevalence of pathogens and their sensitivities to antibiotics in the USA. Accordingly, if the probable source of infection is

the lower gastrointestinal tract or pelvis, meropenem treatment is initiated empirically giving coverage to possible B. fragilis infection; for suspected aerobic Gram negative bacteria tigecycline is started; if the probable source of infection is the genitourinary tract, piperacillin-tazobactam is recommended directed against aerobic Gram negative bacteria or meropenem against Enterococcus faecalis; if the probable source of infection is a central venous line and the probable pathogen is S. aureus, empirical treatment with meropenem is started; in institutions where central line infections due to MRSA are more prevalent vancomycin, daptomycin, or linezolid is recommended; for aerobic Gram negative bacteria tigercycline is prescribed; for nosocomial pneumonia meropenem treatment is started to give broad spectrum coverage inclusive for Pseudomonas aeruginosa, or cefepime for possible aerobic Gram negative bacteria [23].

In other countries or other hospitals with different prevalence of pathogens and different antibiotic sensitivities, different institutional protocols for initiation of empirical antibiotic treatment of sepsis may be useful. Emphasis is given to unit specific choces of empiric antibiotic treatment [3,23,25-27].

General Supportive Measures in the Treatment of Sepsis

Circulatory impairment in sepsis is the consequence of vasodilatation, capillary leak, and reduced myocardial contractility. For volume resuscitation crystalloids and colloids are used, but it remains unresolved whether colloids have an advantage over intravenous crystalloids [17]. Concerning administration of human albumin for volume resuscitation, studies showed that intravenous albumin treatment was associated with a 6% excess mortality or no benefit in outcome [28,29]. Circulatory compromise should be corrected early and effectively, but achievement of this aim is hindered by inaccuracy of the methods which estimate the effective intravascular volume. For guidance most physicians will rely on clinical endpoints such as sustained increase in blood pressure, increase in central venous pressure, decrease in heart rate, increased urine output, improovement of base deficit and blood lactate concentration [17]. However, global hemodynamic parameters do not provide adequate information on tissue perfusion [30]. Furthermore, mixed venous oxygen saturation and blood lactate – the global 'downstream' markers of impaired tissue perfusion - are insensitive indicators of tissue hypoxia [31]. Other indicators of optimal fluid resuscitations are needed. Thoracic impedance monitoring, which allows for early diagnosis of pulmonary congestion and can predict decompensation in patients with heart failure [32,33], has not been sufficiently explored for monitoring fluid resuscitation. Transesophageal Doppler echocardiography [34], as well as pulse contour analysis, provides information on the effect of fluid loading on cardiac output [35]; their value in the management of fluid resuscitation needs to be confirmed by further studies. Monitoring the pulmonary capillary wedge pressure showed no benefit in patients with severe sepsis [17]. In distinction to the shortages of the various methods mentioned above, assessment of the peripheral perfusion allows for very early diagnosis of hypoperfusion in the microcirculation and may become the preferred technique in the setting of intensive care units [28]. Monitoring the course of sepsis by

observing the microcirculation is discussed in more detail in the chapter 'Normotensive Shock'.

Administration of catecholamines is needed when adequate tissue perfusion cannot be achieved by intravenous fluids. Either noradrenaline or dopamine is recommended as first line agent. The quality of evidence is poor for the choice of particular vasopressor agents to support the circulation in sepsis [17]. Dopamine exhibits a graded pharmacological response, with a dose-dependent predominant activation of dopaminergic receptors, β-receptors, and ά-receptors. Generally, at doses <3 μg/ kg/min, dopamine activates dopamine A1 receptors, which dilate the renal arteries and other vascular beds, including mesenteric, coronary, and cerebral vascular beds. Stimulation of dopamine A2 receptors by dopamine leads to inhibition of norepinephrine release from sympathetic nerve endings. Activation of dopamine A1 and A2 receptors also results in a decline in systemic vascular resistance and an increase in renal blood flow [36]. Low-dose dopamine, that has been much used in the past mainly because it increases the splanchnic blood flow, has been proscribed in recent years. Low-dose dopamine does not improve hepatic function, it inhibits gut motility, mediates immunosuppression, impairs thyroid function, and does not prevent renal dysfunction or death [37]. In one study dopamine was associated with an increased risk of death [38]. Authors of the recent international guidelines for management of severe sepsis and septic shock recommend that low-dose dopamine not be used for renal protection [9]. At high doses, dopamine may precipitate supraventricular arrhythmias. The role of non-catecholamine drugs, such as vasopressin, levosimendan, methylene blue, and the phosphodiesterase inhibitors, to support the circulation in sepsis remains to be clarified [17].

The problem of adrenal insufficiency in severe sepsis has focused much interest. Complete adrenal failure is rare in sepsis, but relative adrenal insufficiency is more common. An inadequate response to synthetic corticotrophin (defined as ≤9 μg/dl increase in cortisol level 1 hour after administration of 250 μg ACTH) was found in the majority of patients with septic shock [39]. A 5- to 7-day course of physiologic hydrocortisone doses with subsequent tapering increased the survival rate and shock reversal in patients with vasopressor-dependent septic shock, while short courses of high-dose glucocorticoids decreased patient survival [38]. Two meta-analyses concluded that low dose hydrocortisone for 5 to 11 days in patients with severe sepsis or septic shock significantly reduces the duration of shock and in-hospital mortality [40,41]. One expert opinion suggested that an ACTH stimulation test should be performed and corticosteroid should be started treatment as soon as possible in patients with vasopressor-dependent shock, respiratory failure, and an additional organ failure; subsequently corticosteroids can be discontinued in patients having an adequate response to ACTH [17]. There is disagreement, however, regarding the utility of corticotherapy in patients with sepsis and septic shock and also relative to the use of the ACTH stimulation test to indicate who should receive hydrocortisone treatment. First, adrenal function in the critically ill is a dynamic process, and an appropriate initial adrenal response does not preclude later development of relative adrenal insufficiency [42]. Second, in a number of studies supplementation of corticosteroids did not improve survival in critical illness [43,44]. Authors of the recent international guidelines for management of severe sepsis and septic shock suggested that the ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone [18].

Nutrition requirements during severe sepsis are also subject to controversies. In general, early enteral nutrition is recommended [17]. Nutritional supplements, such as l-arginine and omega-3 fatty acids, unexpectedly increased the mortality in patients with severe sepsis [45,46]. Furthermore, the indication for strict glucose control in septic patients is controversial. Controlled trials of aggressive glycemic control have provided insufficient evidence to justify subjecting patients to the real risks of iatrogenic hypoglycemia [47]. A meta-analysis of the benefits and risks of tight glucose control in critically ill adults showed that tight glucose control is not associated with significantly reduced hospital mortality but is connected with an increased risk of hypoglycemia [48]. A cautious approach to the treatment of hyperglycemia in patients with sepsis has been recommended, with target blood glucose of 144-162 mg/Dl [47].

Immune dysregulation in sepsis is accompanied by a more pronounced procoagulant state [13]. Patients with severe sepsis should receive deep vein thrombosis prophylaxis unless there are contraindications such as active bleeding, recent intracerebral hemorrhage, thrombocytopenia or severe coagulopathy. Either low-dose unfractionated heparin administered twice or three times per day is recommended or daily low-molecular weight heparin. Unfractionated heparin is preferred over low-molecular weight heparin in patients with moderate to severe renal dysfunction [18]. Also, stress ulcer prophylaxis should be provided using a H2 blocker or proton pump inhibitor [18].

Guidelines

The 2004 guidelines on treatment of sepsis and septic shock have been recently updated [18]. Recommendations were graded according to the quality of evidence from high (A) to very low (D) and according to the strength of recommendations. A strong recommendation (1) indicates that an intervention's desirable effects clearly outweigh its undesirable effects (risk, burden, cost). Weak recommendations (2) indicate that the balance between desirable and undesirable effects is less clear. The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. Key recommendations of the 2008 guidelines include: early goal-directed resuscitation of the septic patient during the first 6 hours after recognition (1C); blood cultures taken before antibiotic therapy (1C); imaging studies performed promptly to confirm potential source of infection (1C); administration of broad-spectrum antibiotic therapy within 1 hour of diagnosis of septic shock (1B) and severe sepsis without septic shock (1D); reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate (1C); an usual 7-10 days of antibiotic therapy guided by clinical response (1D); source control with attention to the balance of risks and benefits of the chosen method (1C); administration of either crystalloid or colloid fluid resuscitation (1B); fluid challenge to restore mean circulating filling pressure (1C); reduction in rate of fluid administration with rising filing pressures (1D); vasopressor preference for norepinephrine or dopamine to maintain an initial target of mean arterial pressure 65 mm Hg or more (1C); dobutamine inotropic therapy when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy (1C); stress-dose steroid therapy given only in septic shock after blood pressure is

identified to be poorly responsive to fluid and vasopressor therapy (2C); recombinant activated protein C in patients with severe sepsis and high risk for death by clinical assessment (2B except 2C for postoperative patients). In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, the target hemoglobin should be 7-9 g/dL (1B); a low tidal volume (1B) and limitation of inspiratory plateau pressure strategy (1C) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure in acute lung injury (1C); head of bed elevation in mechanically ventilated patients unless contraindicated (1B); avoiding routine use of pulmonary artery catheters (1A); institution of glycemic control (1B), targeting a blood glucose lower than 150 mg/dL after initial stabilization (2C); equivalency of continuous veno-veno hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1A); use of stress ulcer prophylaxis to prevent upper gastrointestinal bleeding using H2 blockers (1A) or proton pump inhibitors (1B).

Some of the above recommendations may be less suitable for old patients, in particular for frail subjects.

III. Empirical Antibiotic Treatment of Sepsis in Acute Geriatric Care

In our institution, piperacillin-tazobactam is at present the first choice empirical treatment for sepsis of suspected genitourinary origin, for hospital acquired pneumonia, and for sepsis of unknown source. However, if pseudomonas infection is thought to be unlikely, other empiric treatments are considered, for example ertapenem. The efficiency of this routine is illustrated by the case histories of three patients who developed sepsis, while hospitalized for different causes in the geriatric ward during the first week of August 2008. There may be an extra benefit of this routine. Reports in the literature suggest that empiric treatment of sepsis with piperacillin-tazobactam might be a suitable strategy to decrease endemic CEP resistance (controlled gene expression following ectopic integration into the chromosome) by K. pneumoniae and P. mirabilis [49].

Case 1 - piperacillin-tazobactam for suspected hospital acquired pneumonia An 82-year-old woman with Streptococcus viridans endocarditis, severe aortic stenosis, and left heart failure was improving after 2 weeks of intravenous penicillin treatment, when she became confused, with 39.3^{o}C fever and dyspnea. Pulmonary congestion and bilateral alveolar infiltrates were noted on chest X rays. Blood and urine cultures were obtained. In suspecting hospital acquired pneumonia, empirical treatment with piperacillin-tazobactam was started and furosemide was administered intravenously. The fever subsided within 36 hours, the delirium and dyspnea remitted, and the alveolar infiltrates disappeared on chest X rays. E. coli was retrieved from the urine culture, more than 100.000 colonies/cc, resistant to piperacillin-tazobactam but sensitive to ertapenem. The fast clearance of bilateral pulmonary infiltrates after administration of furosemide demonstrated that heart failure was their cause. The diagnosis of hospital-acquired pneumonia turned out to be wrong and urosepsis was the final diagnosis. Though sepsis was obviously remitting, piperacillin-tazobactam was exchanged to ertapenem, which was administered for 5 days. Thereafter, a 4 week course of

penicillin treatment for endocarditis was completed. She was discharged in good condition. Piperacillin-tazobactam was efficient as first line treatment of sepsis in vivo, though bacteriology laboratory data showed a different sensitivity in vitro.

Case 2 - piperacillin-tazobactam efficient in culture-negative sepsis A 91-year-old woman was in good general health until recently, when she was hospitalized with myocardial infarction and E. coli urinary tract infection. Two weeks later, ischemic gangrene of the toe developed and MRSA osteomyelitis of the first metatarsal bone was diagnosed. After surgical debridement of the necrotic tissues she was transferred to our geriatric ward for long-term intravenous vancomycin treatment. Three weeks on vancomycin she became unexpectedly obtunded, hypotensive and temperature increased to 39.6^{o}C. In suspecting sepsis, treatment with piperacillin-tazobactam was started. A few hours later she passed two tarry black stools, became anuric, and was transferred to the intensive care unit. Defeverness followed soon, but renal failure developed with decline of the creatinine clearance to 29 ml/min/m^2. Numerous blood and urine cultures were negative, so empirical treatment with piperacillin-tazobactam was continued. The vancomicin dose was adjusted to the diminished renal function. After completion of a 14 day course, piperacillin-tazobactam was discontinued and specimen for blood and urine cultures were obtained. A spike of fever 39.1^{o}C followed. Piperacillin-tazobactam was re-instituted and the temperature returned to normal, along with hemodynamic stability and improvement of mentation. Again, urine and blood cultures did not show any growth. On further evaluation, echocardiography showed no evidence of valvular vegetations and computerized tomography did not reveal an infectious focus. There was no recurrence of sepsis. The patient refused to undergo gastrointestinal endoscopy.

In this patient, piperacillin-tazobactam was an efficient initial treatment of sepsis and again efficient at the time of sepsis recurrence. No pathogen could be recovered on numerous cultures.

Case 3 - piperacillin-tazobactam unexpectedly effective in treatment of septicemia with carbapenem-resistant Klebsiella pneumoniae An 87-year-old man was admitted to the geriatric ward with delirium. Lately he suffered of diarrhea, and Campylobacter jejuni was recovered from his stool. The diarrhea was successfully treated with ciprofloxacin 500 mg orally b.i.d. for 5 days. The patient's medical history included chronic lymphoid leukemia, arterial hypertension, chronic atrial fibrillation, chronic renal failure and folate deficiency. The latest medications were metoprolol, furosemide, folic acid and ferrous sulphate. At the time of admission to our ward the temperature was 36.5°C, heart rate 74 bpm, respiratory rate 18 breaths per minute, supine BP 160/94 mm Hg, and oxygen saturation 92% on ambient air. He had an altered level of consciousness and disorganized thinking, fluctuating during the course of the day. The body temperature was normal. Routine laboratory tests showed normocytic anemia and moderate renal failure (hematocrit 34%, blood urea nitrogen 45 mg/dL, serum creatinine 1.6 mg/dL). Range-of-motion exercises, assisted ambulation and low-impact resistive exercises of lower extremities were started; the regular medications were continued. On the second week after admission the occurrence of a vesicular eruption characteristic of trigeminal zona zoster was noticed on the patient's face. The temperature remained normal. He was treated with intravenous acyclovir and made an uneventful recovery. The third week in the ward the patient became sleepy, had shaking chills and the temperature rose to 39.4^{o}C. There was neither cough, diarrhea, urinary frequency or skin

eruption. The white blood cell count increased to 16.000/mm^3 with 68% neutrophils, the C reactive protein increased to 84 mg/L; urinalysis and chest X rays were unrewarding. Blood and urine cultures were obtained and empiric treatment with piperacillin-tazobactam was started. The spiking fever remitted on the third day of antibiotic treatment. Urinalysis and urine cultures were unremarkable. Two of the three blood cultures grew carbapenem-resistant Klebsiella pneumoniae, which was insensitive in vitro to piperacillin-tazobactam. The antibiotic susceptibilities of the isolate were confirmed at another laboratory. Because definitive recognition of carbapenem resistance in Klebsiella pneumoniae can be ascertained only by molecular methods [50,51], the isolate was subjected to randomly amplified polymorphic DNA (RAPD) polymerase chain reaction (PCR), PCR amplification and sequencing of the KPC genes. The PCR and sequencing of the KPC genes endorsed the bacteriologic diagnosis by identifying the blaKPC gene in the specimen.

Once more piperacillin-tazobactam was efficient as empirical first line treatment of sepsis, but, as it turned out, it was effective against carbapenem-resistant Klebsiella pneumoniae. The bacteriologic diagnosis was verified by PCR technique, with sensitivity and specificity of the assay approaching 100% [52]. When results of microbiology become available, antibiotic therapy treatment was changed to tigecycline and the patient made an uneventful recovery. The clinical remission on piperacillin-tazobactam was impressive and surprising, a posteriori. That carbapenem-resistant Klebsiella pneumoniae responded well to piperacillin-tazobactam treatment in vivo is not clearly understood.

Learning points:

- The choice of empiric antimicrobial therapy of sepsis depends on the clinical syndrome, underlying disease, susceptibility patterns of pathogens that previously have been documented to colonize or infect the patient, and drug intolerances.
- An emerging consensus emphasizes the importance of local unit-specific antimicrobial sensitivity data in selection of empiric antibiotic treatment.
- It is generally recommended that de-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known**.**

IV. Vancomycin Treatment for MRSA Infections

In 1958, vancomycin was introduced in clinical practice as an agent active against penicillin-resistant Staphylococcus aureus. A few years later, when the new penicillinase-resistant β-lactams methicillin and cephalothin became available, the use of vancomycin decreased, mainly because of and the high rate of toxicity of the initial vancomycin preparations. Later manufacturing procedures improved vancomycin purity and from this time a conmtinual rise in vancomycin use has occurred [53]. New agents with broad Gram positive activity have emerged but none is evidently superior to vancomicin.

Vancomycin is most often prescribed for treatment of serious infections caused by β-lactam–resistant Gram positive organisms, infections caused by Gram positive organisms in patients with serious allergy to β-lactams, and antibiotic-associated colitis that has not

responded to metronidazole or that is severe and potentially life threatening. The bactericidal activity of vancomycin is concentration independent once a concentration of four or five times the MIC for the organism is reached. Vancomycin concentrations achieved in serum in normal volunteers 2 hours after an intravenous dose of 1g are around 25 μg/mL; these levels decrease to 2 μg/mL by 12 hours. Vancomycin is primarily excreted unchanged via the kidneys by glomerular filtration. A linear correlation between creatinine clearance and vancomycin levels is recognized. Vancomycin half life in adults with normal renal function is 4–11 hours, but increases to 6-10 days in advanced reanl failure [54].

Vancomycin treatment is usually started with a fixed loading dose of 25 mg/kg body weight followed by a maintenance dose that typically is 1g at 12 hour intervals in an adult with normal renal function. In patients with decreased creatinine clearance, nomograms and formulas are used to determine the dosing schedule. A convenient approach is to lengthen the interval between two consecutive 1g doses of vancomycin, according to the equation: Interval = normal interval x (86 mL/min ÷ [0.689 × creatinine clearance mL/min + 3.66]). This treatment regimen should result in an approximate vancomycin serum peak value 30 μg/mL and a trough value 7.5 μg/mL. A meta-analysis of randomised controlled trials comparing intermittent intravenous administration with continuous intravenous infusion of the same total dose of vancomycin showed that continuous intravenous infusion may be more efficient [55]. The recommendation to monitor vancomycin serum concentration to optimize efficiency with minimal toxicity is the subject of debate [56-58].

Case 4– vancomycin nephrotoxicity Monitoring vancomycin serum concentration is not always helpful in preventing vancomycin toxicity. This is illustrated in the patient presented in detail in the chapter 'Normotensive shock'. Succintly, a 72-year-old man presenting with MRSA septicemia and L1-L2 discitis was admitted for long-term antibiotic treatment. The patient's medical history included arterial hypertension, ischemic heart disease, congestive heart failure, diabetes mellitus, and mild renal failure. On physical examination, the patient was cachectic, the blood pressure 182/84 mmHg, the heart rate 76 bpm, respirations 16 per minute. maximum temperature 37.6°C, and oxygen saturation 92% on room air. There was hepatojugualar reflux and grade 1 ankle edema. Laboratory tests were remarkable for C reactive protein 230 mg/L, serum creatinine 1.6 mg/dl, albumin 2.8 g/l. The estimated creatinine clearance according to the Modification of Diet in Renal Disease equation and Cockcroft-Gault equation was 45 mL/min/1.73 m^2 and 30 mL/min/1.73 m^2, respectively. Treatment with intravenous vancomycin 1g at 24 hour intervals was administered. Vancomycin trough levels were measured twice per week and were found satisfactory, between 5 and 8 μg/mL. The patient continued to receive his current medications, including aspirin 100 mg/day, carvedilol 12.5 mg/day, ramipril 5 mg/day, furosemide 40 mg/day, spironolacton 12.5 mg/day, simvastatin 20 mg/day and insulin.

Thirty days on vancomycin treatment, the temperature was normal and the C reactive protein decreased to 18 mg/L. However, the patient's heart failure deteriorated, with generalized edema and pulmonary congestion. The estimated creatinine clearance was unchanged. Furosemide i.v drip 160 mg/24 hours was administered. Six days later the serum creatinine had risen to 3 mg/dl and the BUN to 110 mg/dl. The urinary sediment was unremarkable. There was no change in the blood pressure, varying between 124-160/70-82 mmHg. On diagnosing the severe deterioration in renal function, treatment with vancomycin,

furosemid and ramipril was discontinued, and rifampicin treatment was instituted. Gradually, over a period of 10 days the creatinine decreased to 2.6 mg/dl and the BUN to 32 mg/dl. In this patient, advanced age, poor nutritional state, hypoalbuminemia, chronic renal failure, and use of a loop diuretic were preexisting risk factors of vancomycin nephrotoxicity. When additional risk factors came in action, specifically exacerbation of heart failure and administration of large doses of furosemide, an acute worsening of renal failure occurred. Monitoring the serum vancomycin concentration twice weekly was insufficient to predict nephrotoxicity.

Nephrotoxicity associated with vancomycin has been reported since the beginning of its clinical use, and thought to be related, at least in part, to impurities in the early preparations [59]. Modern prospectively designed studies reported an incidence of renal functional impairment between zero and 7%. However, when vancomycin was co-administered with an aminoglycoside the nephrotoxicity rate increased to 14-20% [60,61]. Acute interstitial nephritis associated with vancomycin use has also been reported [62]. Several studies have shoed a higher rate of nephrotoxicity in subjects with vancomycin trough levels greater than 10 μg/mL or 15 μg/mL and investigators proposed that measurement of vancomycin levels in serum should be used to optimize therapy [63]. Others have not found a close correlation between vancomycin serum levels and nephrotoxicity [64,65], as opposed to the fair prediction of toxicity by aminoglycosides serum levels.

An approach to minimize the monitoring of vancomycin serum levels was evaluated in a prospective work comparing two treatment modalities. In the first group, patients with the minimized monitoring regimen were dosed by a nomogram and had the regimens adjusted based on actual body weight, estimated creatinine clearance, and a targeted trough concentration of 5-20 microg/ml; a single trough serum concentration was drawn only after 5 or more days of therapy. In the second group, vancomycin levels were frequently tested and serum peak and trough concentrations served to adjust the daily dose of the antibiotic. No differences were found between the two groups with respect to improvement and cure rates, days to eradication, and nephrotoxicity. Considerable cost savings were achieved for patients dosed by nomogram compared with patients dosed by pharmacokinetics [64]. Based on this data, a number of investigators have taken position against the routine measurement of vancomycin serum levels [65].

There are special circumstances when it is prudent to more frequently measure vancomycin concentrations (Table 1), including patients concomitantly receiving another nephrotoxic agent especially aminoglycosides; patients receiving high-dose vancomycin; subjects undergoing hemodialysis; patients with morbid obesity; in the face of rapidly changing or unpredictable renal function; during prolonged vancomycin therapy (longer than 10 days); concurrent or sequential use of systemic or topical potentially nephrotoxic drugs - cisplatin, cephaloridine, gentamicin, kanamycin, amikacin, neomycin, polymixin B, colistin, paromomycin, streptomycin, tobramycin and viomycin [66,67]. Nephrotoxicity is more frequent in elderly patients than in the young; in one study nephrotoxicity of vancomycin vas noticed in 18.9% of the elderly patients versus 7.8% of younger patients [68]. Concurrent loop diuretic use is significantly associated with vancomycin-associated nephrotoxicity (relative risk 5.0)[66]. In patients receiving continuous infusion vancomycin, a serum steady-state vancomycin concentration ≥28 mg/L increases markedly the risk (OR 21)[69]. A

significantly increased risk of nephrotoxicity was observed among patients receiving ≥4 g/day vancomycin/day (34.6% nephrotoxicity), compared with those receiving <4 g vancomycin/day (10.9%), and compared to patients receiving linezolid (6.7%) [70].

Table 1. Risk factors of vancomycin nephrotoxicity

Advanced patient age
Poor nutritional status
Decreased serum albumin
Dehydration
Hypercalcemia
Kidney disease
Shock
Prolonged treatment
Steady-state vancomycin concentration ≥28 mg/L
Concomitant administration of other nephrotoxic agents
Leukemia
Rapidly fatal illness
Pneumonia
Pleural effusion
Liver disease
Obesity

Under special circumstances when serum vancomycin will be measured, patients should have received a minimum of three vancomycin doses or 48 hours of therapy before testing. Samples for trough concentrations should be obtained within 30 minutes of the next scheduled dose. Samples for peak concentrations should be obtained one hour after the end of the infusion. Traditional trough concentrations of 5 to 10 microgram/mL [71,72] are being reconsidered in view of increasing minimum inhibitory concentrations of staphylococci to vancomycin. Trough concentrations of 10 to 15 microgram/mL are generally recommended [55], but for treatment of deep-seated staphylococcal infections such as endocarditis, prosthetic joint infections, CNS infections trough 15 to 20 microgram/mL are recommended [64,73].

Learning points:

- Most important among risk factors of vancomycin nephrotoxicity are prolonged treatment, concomitant administration of other nephrotoxic agents, advanced patient age, low serum albumin, poor nutritional status, dehydration, kidney disease, shock, and administration of loop diuretics.
- Minimal monitoring of vancomycin therapy by taking a single trough serum concentration after 5 or more days of therapy is safe, as long as the patient is hemodynamically stable.

- In patients with rapidly changing renal function, day-to-day monitoring of serum levels may be advisable.

Case 5 - spurious vancomycin toxicity This case has been described in detail elsewhere [74]. A 56-year-old man was admitted for treatment of sternal osteomyelitis subsequent to coronary artery bypass surgery. On vancomycin treatment, the initial trough vancomycin level was 10.3 μg/mL. Later during the course of treatment, the access to superficial veins became difficult and a central PermCath venous catheter was inserted via the axillary vein to provide venous access. A few days later, the trough vancomycin level was 62 μg/mL in a blood sample obtained via the PermCath. The patient was symptom free and the plasma creatinine was 0.8 mg/dL. Vancomycin administration was discontinued. Sixteen hours later, vancomycin trough was 120 μg/mL in blood drawn trough the PermCath. On the same day, repeated sampling produced vancomycin trough level 43.4 μg/mL in blood drawn via the PermCath, while blood drawn at the same time by puncturing the femoral vein showed vancomycin 10.1 μg/mL. This observation was replicated on the following day. Flushing the PermCath with 10 ml or 50 ml of saline did not eliminate the vancomycine from the line. Thus, samples of saline removed from the line (after its rinsing out) or blood removed via the line contained high concentrations of vancomycin. Unvariably, 'toxic' vancomycine levels were related solely to the PermCath line. The simple and obvious explanation to spuriously toxic vancomycin levels in this patient may be that vancomycin was adhering to the venous catheter.

Learning point:

- Spuriously ‘toxic’ vancomycin levels may arise by drawing blood through venous lines.

Case 6 – vancomycin induced neutropenia A 79-year-old woman received vancomycin after removal of an infected hip prosthesis. MRSA was cultured in a specimen acquired from the wound at the time of surgery. The patient’s medical history included osteoarthritis and arterial hypertension. Her regular medications were ramipril, hydrochlorothiazide, simvastatin, aspirin and oxycodone. Vancomycin treatment was administered intravenously 1g at 36 hour intervals and the once measured trough level was 2.2μg/mL. The serum creatinine was 1.2 mg/Dl. The clinical response was favorable; after 4 weeks of treatment the temperature was normal and the C reactive protein was 12 mg/L. At this time point, a fall in the white blood cell count was witnessed from 11200/mm^3 with 82% neutrophils to 3400/mm^3 white blood cell with 1150/mm^3 neutrophils and no band forms. The hemoglobin was 11g/dL and the platelets 230000/mm^3, essentially unchanged. The C reactive protein was 10.2 mg/L. Common causes of selective neutropenia could be eliminated, mainly infections and a variety of drugs, thus the possibility that vancomycin caused this patient's neutopenia was considered. Vancomycin was replaced with rifampin and fusidic acid. Within 3 days the neutrophil count increased to 1620/mm3 and after one week to 3100/mm^3, the total white blood cells were 6040/mm^3. The subsequent course was uneventful.

Although unusual, neutropenia associated with vancomycin therapy may occur, with a frequency of about 1% to 2%. This rate increases with long-term vancomycin administration.

Neutropenia usually resolves after discontinuation of the drug. In the case described by Mackett et al. [75] neutropenia was noticed on day 17 of vancomycin treatment, it progressed over the next 3 days, and after discontinuation of vancomycin a rise in the neutrophil count occurred within 5 days of discontinuation. This is not unlike to the course of neutropenia in the patient treated by us. In a patient described by Koo et al. [76], severe leukopenia developed on vancomycin with the presence of only occasional neutrophils in the peripheral blood. On discontinuation of vancomycin, the leukocyte and neutrophil counts promptly increased with full recovery after a week. Subsequently, the patient was restarted on a five-day course of vancomycin at a lower dose, that was uneventful, without recurrence of neutropenia. The latter observation is in disagreement with the commonly held concept that an immunologic mechanism may be responsible for the reaction. Vancomycin-induced neutropenia may occur more often than previously reported. The rate was 13% in patients treated with vancomycin for a mean of 6.2 months [77]. In another study, 14 of 114 (12%) patients treated with vancomycin developed vancomycin-induced neutropenia, including 4 cases with absolute neutrophil counts $\leq$500 cells/mm^3. The mean duration of vancomycin therapy and time to neutropenia were 32 days. Resolution of vancomycin-induced neutropenia occurred promptly after discontinuation. There was no correlation between total vancomycin doses and serum concentrations with development of neutropenia. The authors concluded that clinicians should monitor the blood cell count at least weekly in patients receiving vancomycin therapy for longer than 2 weeks [78]. Vancomycin-induced neutropenia was reversible by administration of granulocyte colony-stimulating factor in two patients receiving long-term vancomycin therapy as outpatients [79].

Learning points:

- Neutropenia may occur on long-term vancomycin treatment.
- Vancomycin-induced neutropenia may be severe.
- Resolution occurs promptly after discontinuation of vancomycin.
- Blood cell count should be monitored at least weekly in patients receiving vancomycin therapy for longer than 2 weeks.

The recognition of the shortcomings of vancomycin as an antistaphylococcal agent, together with the availability of alternative effective antistaphylococcal antibiotics, has led to a reassessment of its role therapeutics. Evidence suggests that vancomycin may be inferior to some comparator agents in the treatment of infections due to MRSA. This, together with the problem of heteroresistance to vancomycin, as well as poor tissue penetration after its systemic administration, presents potential obstacles to the successful therapy of S. aureus infections with vancomycin. While it was implied that these problems may be overcome by administration of much higher doses of vancomycin, the efficacy and safety of the proposed high dosre schedule remains to be proven by randomized clinical trials.

In the last few years new anti-MRSA drugs have been registered [80,81], such are linezolid the most widely used new anti-MRSA agent, quinupristin-dalfopristin, daptomycin, a novel lipopeptide, active on germs both in the replicating and in the resting phase, and tigecycline, the first approved glycylcycline. Other drugs from different classes are in development and will further enhance in the next few years our therapeutic armamentarium:

three glycopeptides (dalbavancin, telavancin, and oritavancin), two broad spectrum cephalosporins, ceftobiprole and ceftaroline, iclaprim, a diaminopyrimidine, as well as a carbapenem, CS-023/RO-4908463, and adjuvant therapies such as the monoclonal antibody tefibazumab. Despite the fact that these newer agents have been compared with vancomycin in trials only designed to demonstrate noninferiority, some potential evidence of superiority over vancomycin has emerged.

V. Containment of Infection with Resistant Strains

Antimicrobial resistance in health care-associated pathogens is a growing problem [22,26,82]. A recent shift in the epidemiological profile of methicillin-resistant Staphylococcus aureus has resulted in increased rates of health care-associated infections and also in community-associated infections [83]. There is growing resistance of Staphylococcus aureus to vancomycin [84]. The rate of vancomycin resistance among Enterococcus faecium has also increased [85]. Multidrug resistance in Pseudomonas aeruginosa is rising. Carbapenem-resistant Klebsiella strains have emerged [22]. Acinetobacter species are increasingly resistant to carbapenems and third-generation cephalosporins. A hypervirulent strain of Clostridium difficile has increased resistance to fluoroquinolones. An alarming escalation of hospital-acquired infections due to multi-drug resistant Gram negative bacteria has occurred. Pseudomonas aeruginosa or Acinetobacter baumanii isolates found to be resistant to all commonly used antibiotics are now treated with older drugs such as colistin or combinations of antibiotics.

In acute geriatric care, skillful use of antibiotics and the undertaking of infection containing are difficult, perhaps more than in other settings. Principles of containment of infection with resistant bacterial strains have been summarized under the auspices of the Centers for Disease Control and Prevention's in 2006 [86]. In essence, persistence of the resistant strain in a healthcare setting is dependent on the presence of vulnerable patients, antimicrobial use, increased potential for transmission from colonized or infected patients, and implementation of prevention efforts. Patients vulnerable to colonization and infection include those with severe disease, especially those with compromised host defenses from underlying medical conditions, recent surgery, or indwelling medical devices. Multidrug-resistant organisms are carried from one person to another via the hands of health care providers. Hands are easily contaminated during the process of care-giving or from contact with environmental surfaces in close proximity to the patient. Without adherence to hand hygiene and glove use, health care providers are likely to transmit multidrug-resistant organisms to patients. Universal precautions should be used for all patients during contact with blood, body fluids, or secretions, i.e. wearing gloves, spectacles and impermeable gowns if aerosol or splash is likely. Aggressive isolation is recommended to restrict spread of resistant organisms and their plasmids for MRSA, VREF and highly resistant gram-negative organisms. The contact precautions can be discontinued when three or more surveillance cultures for the target multi-drug resistant organism are repeatedly negative over the course of a week or two in a patient who has not received antimicrobial therapy for several weeks

[86]. Thus, strategies to increase and monitor adherence are important components of multidrug-resistant organisms control programs [86].

For containment of infection with resistant strains, application of barrier precautions has been shown to be highly efficient [87-89]. Here are some examples. A control program to prevent the spread of multi-resistant bacteria in a teaching hospital focused on methicillin-resistant MRSA and enterobacteriaceae producing extended-spectrum beta-lactamases (ESBL); the intervention was based on washing hands with antiseptic soaps, wearing disposable gloves and gowns, and identifying carriers of multi-resistant bacteria [89]. The incidence of infection decreased by 17.9% for MRSA and by 54.9% for ESBL. The decrease of the incidence concerned both resistant and susceptible strains. In nursing homes, aggressive containment practices are also efficient in reducing colonization rates. In a nursing home, the initial colonization rate with MRSA was 52% among residents. To decrease colonization and infection rates and to prevent the introduction of additional colonized patients into the closed environment, a program was initiated comprising total population and staff surveillance and aggressive containment measures (contact isolation, baths with chlorhexagluconate, treatment of nasal carriers with bacitracin and treatment of both colonized and infected patients). This was followed by maintenance measures of screening new admissions for MRSA with contact isolation and treatment for positive cases as described during the aggressive phase. Total population surveillance was repeated after one year. After one year the colonization rate dropped to 2% and the infection rate to 1.4%, no employees were colonized with MRSA. This reduction was maintained over time [90].

Elaboration of institutional guidelines for prevention of transmission of multidrug-resistant organisms are an imperative need. Examples of such guidelines [91] recommend performance of active surveillance cultures for patients after admission to health care facilities or to high-risk-patient care units, to detect colonization with target multidrug-resistant organisms. Patients who are colonized with these potential pathogens are placed under contact precautions to prevent transmission to other patients. Such screening programs raise ethical considerations of restricted autonomy, and require education of patients, family members and visitors. Yet, there is a lack of consensus among recommended infection control guidelines [92] and little is known about the occurrence of multidrug-resistant organisms among home care and hospice patients [8].

Application of the guidelines for management of multidrug-resistant organisms may be particularly difficult in the setting of acute geriatric ward, where patients are often confused or demented, and their elderly visitors may have limitations in understanding the recommendations and in cooperation. It is a difficult to achieve must.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter VII

Erysipelas, Cellulitis and Mimickers

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Skin and soft tissue infections are common in the general population. Their frequency increases in older persons because the decline of the skin's integrity and immunosenescence, as well as the presence of underlying skin conditions and morbidities which increase the risk for skin and soft tissue infections [1-3]. In fact, the skin of elderly persons is structurally and functionally different from that of other age groups. The epidermis is thinner and has a slower cell turnover rate, resulting in less resistance to external injury and prolonged wound healing. Changes in dermal collagen and elastin (their expression is wrinkles) are associated with increased skin fragility. Diminished water-binding capacity of the stratum corneum and decreased function of the eccrine and sebaceous glands result in skin dryness and pruritus. The blood flow is reduced, particularly in the presence of atherosclerosis, hypertension and diabetes mellitus; decrease blood flow to the skin decreases the skin's ability to oppose infection, slows healing and increases xerosis. Sweating is reduced and so the skin becomes more xerotic. Xerosis undermines the integrity of the integument and provides portals for the entry for infections.

The proportion of people with significant skin disorders increases linearly with age. At age 70 years about 70% of the population has at least one skin problem. In parallel, the morbidity and mortality caused by skin and soft tissue infections are increased two-to three fold in the elderly [4,5]. The types of organisms that cause primary skin and soft tissue infections include bacterial, viral and fungal pathogens as well as parasites. In particular, outbreaks of cellulitis caused by group A β-hemolytic streptococci associated with bacteremia have been reported in nursing homes [6]. Because many of these infections may be fatal, cutaneous infections in elderly patients need to be treated promptly. However, the diagnosis of infections and infestations of the skin in the elderly may be difficult because of atypical presentations and underlying chronic skin disorders [7].

In practice it is important to distinguish between three types of acute bacterial infections involving the skin and subcutaneous tissues: infections of the superficial skin layers (erysipelas), infections which involve the dermis and hypodermis (cellulitis), and infections affecting the deep subcutaneous tissue, superficial fascia and underlying muscle [8]. In general, the three types of cutaneous infection differ by their clinical features, epidemiology, risk factors, causative organisms, treatment and prognosis. Yet, the clinical appearance in the initial stages may be undistinguishable.

I. Erysipelas

Erysipelas is a type of cellulitis caused by infection of the superficial layers of the skin and cutaneous lymphatics, clinically characterized by redness, induration, and sharply demarcated, raised borders [1]. Formerly, erysipelas involved most commonly the face. Now, 70% to 80% of the lesions occur on the lower extremities, and only 5% to 20% are localized on the face or ears [5]. Erysipelas is almost always caused by group A streptococci (uncommonly, by group C or G streptococci) [8]. Very rarely, similar skin lesions are caused by Staphylococcus aureus or other bacteria [1-3]. The pathogen enters the skin at sites of local trauma, abrasions, psoriatic lesions, eczema, tinea lesions, but often through apparently intact skin. Predisposing factors are venous stasis, lymph stasis, edema, paraparesis, diabetes mellitus, nephrotic syndrome and alcohol abuse. Because erysipelas produces lymphatic obstruction, and because lymph stasis predisposes to erysipelas, a vicious circle may develop causing recurrences of erysipelas in the previously involved areas. The recurrence rate of erysipelas was about 30% in one study during a 3-year period, being even higher in individuals affected by venous insufficiency or chronic lymphedema [9].

By usual microbiological methods the causative agent can be identified only in a small proportion of patients: 5% of affected persons have streptococcal bacteremia; in 20% of cases streptococci of groups A, C, or G can be isolated on throat culture [9]; asymptomatic anal colonization with group A or G streptococci may be present and serve as a reservoir in individuals with relapsing erysipelas or cellulitis [10]; when erysipelas occurred as a complication of infected skin ulcers, positive isolates of group A streptococci were obtained from the ulcerated area in 30% of the cases. However, by direct immunofluorescence and cultures of punch biopsy specimens corroborated with serologic titers, evidence of streptococcal infection (groups A, G, and C) was found in 26 of 27 patients with clinical erysipelas [11].

Uncomplicated erysipelas is confined to the dermis and lymphatics. The area of inflammation is bright red, edematous, indurated, with a sharply defined, advancing, raised border, and distinct demarcation between the involved and the normal skin. Lymphangitic 'streaking' is prominent. High fever is common. The diagnosis is usually made by the characteristic clinical setting and appearance. Bacteriologic examinations from needle aspiration, skin biopsy and blood culture are useless in patients with typical features of erysipelas, because positive results are rare [3]. As a rule, erysipelas can be readily distinguished from cellulitis. Occasionally erysipelas extends more deeply causing genuine cellulitis or in extreme may complicate with subcutaneous abscess formation or necrotizing

fasciitis. Bullous erysipelas is another complication of erysipelas, manifesting with intraepidermal bullae; the blister fluid is sterile before erosion and secondary contamination take place [12].

Lesions closely resembling erysipelas may occur in patients with familial Mediterranean fever, but the clinical context is different. Diffuse inflammatory carcinoma of the breast may mimic low-grade erysipelas of the ches wall. Early facial herpes zoster may resemble facial erysipelas but can be distinguished by neuralgic pain and hyperesthesia preceding the herpetic skin lesions. Contact dermatitis or giant urticaria may bear a resemblance with erysipelas but can be distinguished from the latter by normal body temperature and the accompanying pruritus [3,8].

Treatment of erysipelas is mostly empirical. Antibiotics aimed at streptococci are the first choice of treatment in typical cases of erysipelas or cellulitis [8]. Mild early cases of erysipelas may be treated with intramuscular procaine penicillin (600,000 units once or twice daily), penicillin V (250 to 500 mg orally every 6 hours) or erythromycin (250 to 500 mg orally every 6 hours). For more extensive erysipelas it was common practice that patients are hospitalized and receive parenteral aqueous penicillin G (2,000,000 units every 6 hours). Currently there is a trend to avoid hospitalization of patients suffering from erysipelas by promoting intravenous treatments at home, for economic reasons [13]. However, in a study only a third of patients were suitable for home treatment and the majority were admitted to hospital because of severity of their disease or comorbidities [14].When the differentiation between erysipelas and deeper cellulitis is unclear, intravenous administration of a penicillinase-resistant penicillin (nafcillin or oxacillin) or a first-generation cephalosporin is recommended [1,2,15]. The optimal duration of antibiotic treatment for erysipelas is uncertain. A randomized study suggested that the duration of treatment can be shortened to 5 days, since a 5-day course of treatment was as effective as a 10-day course [16]. It might be safer to reserve short-course treatment to patients with obvious clinical improvement by the fifth day and only under close follow-up of the patients [8]. Prognosis is good with antibiotic treatment, but recurrences are common.

For prevention of recurrences, continuing administration of long-acting penicillin is advised based on prospective studies that validated the efficiency of this strategy. By providing antibiotic prophylaxis to patients with multiple previous recurrences of erysipelas, after 1 year or prophylaxis 84% of patients were free of recurrence and after 2 years antibiotic prophylaxis 72% of patients were recurrence-free [17]. Women with arm lymphoedema following mastectomy, having a history of three o more recurrences of erysipelas of the affected arm, were administered benzathin–penicillin G intramuscularly at 14-day intervals; 74% were free of recurrent erysipelas after 1 year and 64% were free of recurrence after 2 years [18]. When nevertheless erysipelas recurs in spite of antibiotic prophylaxis, the issue of compliance with the prophylactic regimen should be addressed. Next, efforts should be made to confirm the diagnosis and to isolate the causative microorganism. Based on this information, the right antibiotic, with adequate dosing and timing, can be selected [19].

Not last, treatment of lymphoedema is an essential issue in the prophylaxis of erysipelas recurrences [20]. In fact, patients presenting with a first episode of erysipelas of the calf often have signs of pre-existing lymphatic impairment, notably not only in the affected leg but also in the other clinically not affected leg. This has been demonstrated by injecting Tc-99m-

labelled human serum albumin subcutaneously in the first web space of both feet [21]. Lymph drainage was quantified as the percentage uptake of Tc-99m-labelled human serum albumin in the groin nodes at 2 h after injection. This study showed that lymphatic drainage in the nonaffected limb was only slightly better than in the limb affecte by erysipelas. Because subclinical lymphatic dysfunction may be an important predisposing factor for erysipelas occurrence and recurrence, it has been recommended that lymph stasis be treated in both legs [21].

Learning points:

- The diagnosis of erysipelas is made according to the clinical appearance of the lesion (bright red, edematous, with distinct demarcation) and the clinical context.
- Atypical erysipelas is sometimes confused with cellulitis.
- Lesions closely resembling erysipelas may occur in patients with familial Mediterranean fever, however in a different clinical context.
- Early facial herpes zoster may resemble facial erysipelas, but neuropathic pain is more severe and preceds to cutaneous herpetic eruption.
- Diffuse inflammatory carcinoma of the breast may mimic low-grade erysipelas.
- Treatment of erysipelas is mostly empirical, based on penicillin.
- When differentiation from deeper cellulitis is unclear, intravenous nafcillin, oxacillin or a first-generation cephalosporin is recommended.

II. Cellulitis

Cellulitis is an acute spreading infection of the skin, extending more deeply than erysipelas to involve the subcutaneous tissues, and is characterized by erythema, warmth, and tenderness of the area involved, but lacking the distinctive anatomical features described for erysipelas. Cellulitis occurs most frequently in diabetics, immunocompromised hosts, and patients with venous and lymphatic compromise and is found near skin breaks. Most cases of cellulitis are caused by β-hemolytic streptococci. Other microorganisms may be involved under specific circumstances: erysipelas that arises at the site of cat or dog bites is typically caused by Pasteurella species, cellulitis following immersion in fresh water is usually caused by A. hydrophila, while cellulitis following immersion in salt water is commonly caused by Vibrio species [3]. Often, the anatomical site of involvement is suggestive of a particular causative agent: periorbital cellulitis is usually caused by streptococcus or staphylococcus; orbital cellulitis (a medical emergency its hallmark being limitation of eye movement) is caused by streptococcus or staphylococcus; perianal cellulitis by staphylococcus; crepitant cellulitis by anaerobic bacteria, group A streptococcus or clostridia; puncture wound cellulitis by pseudomonas; foot cellulitis may be caused by multiple organisms (look for tinea pedis); calf cellulitis by multiple organisms (look for venous insufficiency or lymphedema); cellulitis following cat scratch is caused by Bartonella Henselae; cellulitis in immune compromised patients is often caused by Gram negatives organisms; community-associated methicillin-resistant Staphylococcus aureus strains are more likely to present with abscesses and furunculosis in addition to cellulitis, and can usually be distinguished from streptococcal

infections [20]. The clinical presentation and patient symptoms are usually sufficient for an accurate diagnosis. Obtaining blood cultures is little informative because of their very low yield [22]. Needle aspirations and skin biopsies may be worthwhile for patients with diabetes mellitus, malignancy, or unusual predisposing factors such as immersion injury, animal bites, neutropenia, and immunodeficiency [23]. More cultures and susceptibility tests need to be done in the face of increasing antimicrobial resistance. There are rapid assays that will be available to detect and distinguish methicillin-susceptible and methicillin-resistant strains from clinical specimens within a few hours instead of days [24].

When the clinical presentation is atypical or the response to antibiotic treatment is inappropriate, the diagnosis should be reassessed [25]. Lack of clinical response may be due to unusual organisms, resistant strains of staphylococcus or streptococcus, or extension of infection to deeper tissues in case of necrotizing fasciitis or myositis. Patient compliance with treatment should be ascertained. Physicians should bear in mind the differential diagnosis with noninfectious causes of cellulitis. Disorders which can masquerade as cellulitis are *deep venous thrombosis* presenting as unilateral leg edema, warmth, or erythema, all of which may be confused with infection [26]; *contact dermatitis*, especially in the acute form [27]; *insect stings* which may trigger an extensive regional reaction that may resemble infectious cellulitis [28]; *eosinophilic cellulitis* (Wells syndrome) characterized by acute pruritic dermatitis and eosinophilia [28]; *erythema nodosum* may sometimes present as a large solitary erythematous lesion resembling infectious cellulitis [29]; *lipodermatosclerosis* is a form of panniculitis that complicates venous insufficiency and its acute form could masquerade as cellulitis [30]; *panniculitis of various etiologies* (α_1-antitrypsin deficiency, lupus panniculitis, postirradiation panniculitis, Weber–Christian disease, cytophagic histiocytic panniculitis, post-steroid panniculitis, and nodular panniculitis) may sometimes be confused with infectious cellulitis [31-33]. In rare cases, *lymphoma* presents as cellulitis [34]. Other disorders that may masquerade as cellulitis are *lymphedema*, *sarcoidosis*, *subcutaneous plaques* in polyarteritis nodosa, *pyoderma gangrenosum* and *Sweet's syndrome* [35,36].

Ancillary measures in the treatment of cellulitis include elevation and immobilization of the affected segment, cool sterile saline dressings on open lesions to remove purulence, topical antifungal medications for interdigital tinea, support stockings in patients with peripheral edema, and skin hygiene [36]. A penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin is given empirically, unless streptococci or staphylococci in the community are resistant to these agents. For penicillin-allergic patients, clindamycin or vancomycin is recommended [3]. In a few patients, the cutaneous inflammation worsens after initiating antibiotic treatment, probably because the enhanced release of enzymes by the pathogen under the effect of bactericidal antibiotics [3].

Management of complicated cellulitis is beyond the possibilities of the geriatric ward. There are clues to a potentially severe deep sited soft-tissue infection: pain disproportionate to the physical findings, violaceous bullae, cutaneous hemorrhage, skin sloughing, skin anesthesia, rapid deterioration of general symptoms or aggravation of the cutaneous lesion, and gas in the tissues [3].

Learning points:

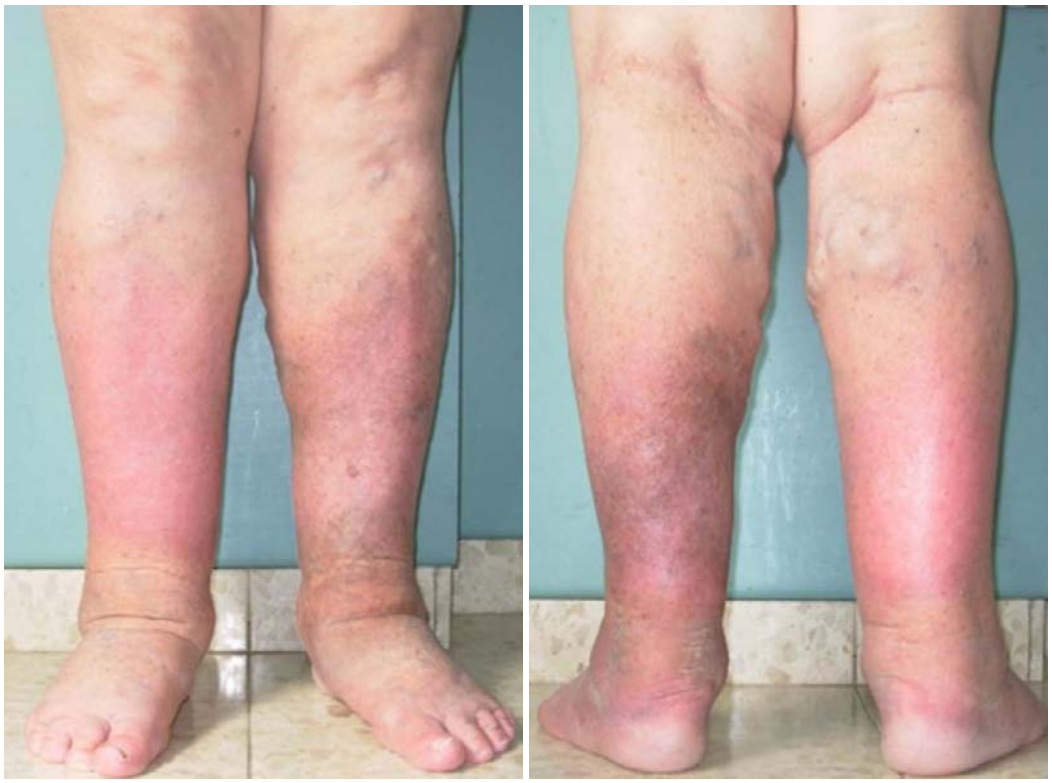
- Cellulitis is an acute spreading infection of the skin involving the subcutaneous tissues. It lacks the distinctive anatomical features described for erysipelas.
- Most cases of cellulitis are caused by β-hemolytic streptococci.
- Blood cultures are little informative because of their very low yield and antibiotic treatment is started empirically.
- A penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin is recommended, unless streptococci or staphylococci resistant to these agents are well-known in the community.
- When the clinical presentation is atypical or when a patient fails to respond to appropriate therapy, a search for a deep-seated infection, foreign body–related infection, or depressed immune state should be initiated.
- Conditions which may masquerade as cellulitis are deep venous thrombosis, contact dermatitis, eosinophilic cellulitis, plaque-like erythema nodosum, and panniculitis of various etiologies.

III. Case Histories

Three case histories are presented, illustrating frequently encountered situations in acute geriatric care. Yet, their management is not devoid uncertainties.

Case 1 - acute cellulitis complicating lipodermatosclerosis of chronic venous disease. A 70-year-old woman was referred to hospital for fever and painful swelling of her right calf. For many years she suffered of swollen feet, varicous veins and recurrent erysipelas of the calf. She was currently on no medication and neglected to wear the prescribed compression stockings. On physical examination, the temperature was 38.9^{o}C, the blood pressure 166/82 mmHg, the heart rate 92 bpm, respirations 18/min. There was grade 2 edema of the dorsum of the feet and ankles, abundant reticular veins, protuberant and engorged calf veins with downward-going impulse on coughing. Her right calf was swollen. The skin in the distal part of the right calf was shiny-pink, tender and felt warm on palpation. At the time of admission there was no distinct demarcation between the erythematous and the normal skin, but two days later the demarcation line became clear. On both calves, the skin and subcutaneous tissues were thickened and indurated, in a sleeve-like distribution beginning about 10 centimeters distal to the knees; the indurated areas were not exactly matching the congested or hyperpigmented areas. Ancillary laboratory tests showed white blood cells 18.100/mm^3 and C reactive protein 153 mg/L. Duplex ultrasonography with the patient supine showed engorged deep and superficial veins in the thighs and calves and venous reflux; the veins were easily compressible; no luminal clots or anatomic causes of external compression were apparent. At this point the clinical diagnoses' were acute cellulitis of the right calf, bilateral lipodermatosclerosis of calves, and chronic venous insufficiency. Empirical treatment with cloxacillin 500 mg every 6 hours was started. Leg elevation and compression stocking with a gradient of 30-40 mm Hg were recommended. After 4 days the body temperature returned to normal; there was some fading of the erythema and swelling on the right calf. Blood cultures,

taken before the antibiotic treatment, were negative. After 10 days of antibiotic treatment, swelling and erythema were still evident (Figure 1) while the patient was comfortable except for pruritus and a dull discomfort in the right calf. At discharge, the patient was advised to wear compression stockings and to consult a phlebologist in considering ablation of the varicous veins. Oral penicillin for prophylaxis of erysipelas recurrence was prescribed. This case brings in focus several issues of practical importance.



a b

Figure 1. Large varicous veins in the calves, numerous perimaleolar reticular veins, chronic lipodermatosclerosis and acute cellulitis of the right calf.

First, cellulitis may be confused with *deep venous thrombosis* a real problem in the early hours after onset of the symptoms. Both disorders present with unilateral leg edema, warmth or erythema. The occurrence of chills or high fever from the beginning makes deep venous thrombosis unlikely, rather the diagnosis of sepsis is suspected. Local signs of cellulitis may by now be present or may become apparent within 24 hours [26].

Second, *concurrent onset of cellulitis and deep vein thrombosis* is a difficult diagnosis that should not be missed because of serious consequences. A true association between deep vein thrombosis and cellulitis has been reported with frequency ranging from 0 to 15% [37-39]. In a prospective study on this topic, a systematic search for deep vein thrombosis was performed among 431 consecutive patients with cellulitis of the leg; deep vein thrombosis was revealed in 3 instances [38]. The authors concluded that a systematic search for deep vein thrombosis is not warranted in patients with leg cellulitis. However, when prothrombotic

risk factors are present in a patient with leg cellulitis, such as immobilization, previous thromboembolism, intravenous injection of illicit drugs [40], septic phlebitis [41], chemotherapy through central venous lines or after endovenous laser treatment [42], it may be reasonable to perform a Doppler ultrasound examination for deep vein thrombosis.

Third, the *accuracy of Doppler ultrasound* in certain settings may be suboptimal. Venous insufficiency is a common cause of false-negative ultrasound results in acute venous thrombosis. Therefore, repeated examinations of the lower extremities by ultrasound should be considered to improve the diagnostic accuracy [43].

Fourth, *infectious cellulitis may be confused with a flare of lipodermatosclerosis*. Lipodermatosclerosis is a form of chronic non-infectious cellulitis that complicates venous insufficiency. The clinicopathologic findings of lipodermatosclerosis are similar or identical to the disease previously reported as chronic indurated cellulitis, hypodermitis sclerodermiformis, or sclerosing panniculitis [44]. Lipodermatosclerosis is a consequence of prolonged high pressure in veins, the deposition of fibrin around capillaries, and consequent impaired O_2 diffusion [23]. Leucocytes become 'trapped' in small veins and capillaries of the leg during periods of venous hypertension produced by sitting or standing. Entrapped neutrophils become degeranulated as shown by increased plasma levels of neutrophil granule enzymes during periods of venous hypertension. Soluble parts of the endothelial adhesion molecules VCAM, ICAM, and ELAM are elevated in patients with venous hypertension and further increase following 30 minutes of standing. These data imply that venous hypertension causes neutrophil and monocyte activation, which in turn causes injury to the endothelium. Perivascular inflammatory cells stimulate fibroblasts in the skin leading to tissue remodeling and laying down of fibrous tissue. Vascular endothelial growth factor stimulates proliferation of capillaries within the skin [45,46]. The latter inflammatory and fibrosing alterations involve the panniculus adiposus, superficial fascia and perimysium. Histologically, they are similar to the inflammatory and fibrosing changes observed in eosinophilic fasciitis and its variants [47,48].

Lipodermatosclerosis comprises a broad spectrum of clinical and pathological manifestations, ranging from an acute inflammatory phase to the chronic fibrotic phase. Chronic phase lipodermatosclerosis is characterized by induration, a permanent brown-red to violet discoloration of the skin, and an 'inverted wine bottle' configuration of the calves. The diagnosis is easily established on clinical examination and there is usually no need for histological confirmation of the diagnosis. Because lipodermatosclerosis can lead to poor healing of wounds, biopsies should be avoided [49].

Acute lipodermatosclerosis presents with erythema, warmth, tenderness and swelling of the calf, and equally manifest acute exacerbations of chronic lipodermatosclerosis; any of these cab easily be confused with infectious cellulitis. Severe pain is the leading symptom and patients with 'acute lipodermatosclerosis' [50]; the patients are often unable to tolerate compression therapy, as also observed in our patient. Proper recognition is important to avoid unnecessary treatments and diagnostic procedures, and because acute lipodermatosclerosis responds rapidly to stanozolol. Although acute lipodermatosclerosis generally lasts a few months, occasionally the course is more prolonged lasting more than a year [49]. Yet, the discrimination between acute lipodermatosclerosis and infectious cellulitis is uncertain. We could not find in the literature studies on this topic. In facing such a dilemma clinicians often

prescribe a course of antibiotic treatment and if remission of fever occurs within 2 to 4 days, the favorable response is ascribed, by right or not, to antibiotic effect. So it was in the patient described above.

Fifth, *lipodermatosclerosis constitutes an important health problem* because of its high prevalence as well as the resulting disability and expenses. Lipodermatosclerosis is estimated to occur in up to 7% of the persons more than 50 years of age, more often in women. The mainstay of treatment is to control leg edema. Leg elevation and compression stocking with a gradient of 30-40 mm Hg are considered the basics of the treatment in chronic venous insufficiency [51]. Noncompliance, however, is very frequent, regardless of age, sex, etiology of chronic venous disease, duration of symptoms, or disease severity. The main reasons for noncompliance are wear-discomfort and a sense of restriction imposed by compressive stockings [51]. There is little evidence base concerning the pressure necessary to be applied, dosimetry of compression to be performed, for how long and at what level compression should be applied, and concerning the possible different outcomes by applying elastic or short-stretch compression [52]. In patients with acute stasis dermatitis, a compression Unna boot can be applied. Topical corticosteroid creams or ointments are used frequently to reduce inflammation and itching. Superimposed infections are the result mostly of Staphylococcus or Streptococcus organisms and should be treated with suitable antibiotics.

For acute lipodermatosclerosis, use of compression gradient stockings or an intermittent pneumatic pump may be helpful if tolerated. Nonsteroidal anti-inflammatory agents are sometimes of benefit and safer than corticosteroids. Stanazol, an anabolic steroid given over 8 weeks, effectively alleviated pain and reduced dermal thickness in patients with acute lipodermatosclerosis [53]. More recently, dapsone has been found to be effective. Sclerotherapy is efficient for the treatment of acute lipodermatosclerosis. Usually, skin inflammation decreases within a week after sclerotherapy. Standard surgical methods, i.e. interruption of reflux in the superficial and perforating veins and procedures involving the ulcer are beneficial at any stage [54,55].

Learning points:

- Chronic venous insufficiency predisposes to occurrence of calf erysipelas or cellulitis.
- Chronic venous insufficiency also predisposes to a chronic, low-grade, non-infectious cellulitis called lipodermatosclerosis.
- Chronic venous insufficiency also predisposes to acute lipodermatosclerosis or flares of chronic lipodermatosclerosis, which may resemble erysipelas; the differential diagnosis between acute lipodermatosclerosis and erysipelas is empirical and unsure.

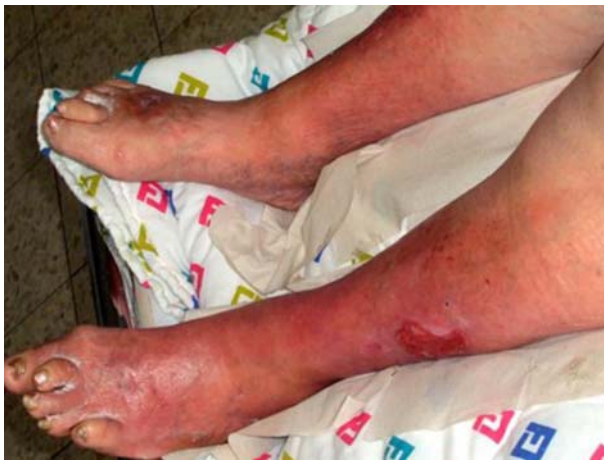
Case 2 - Stasis dermatitis with dependent cyanosis and edema An 84-year-old woman presented with a 10-day history of burning sensation in the distal part of the calves and an emerging shallow ulcer on the left calf. The body temperature was normal. Swab cultures from the skin ulcer grew pseudomonas aeruginosa. Treatment with ciprofloxacine was started and the patient was referred to our department of acute geriatric care. The patient's medical history was remarkable for recurrent erysipelas of the calves, aortic stenosis and regurgitation, chronic atrial fibrillation, moderate pulmonary hypertension, tricuspid

regurgitation, hiatal hernia, hyperthyroidism, osteoporosis, and a breast biopsy that revealed atypical ductal hyperplasia. She was a non-smoker and abstained from alcohol. She was regularly treated with warfarin, propafenone hydrochloride 450 mg, propil-thiouracil 50 mg, hydro-chlorothiazide 25 mg, omeprasol 20 mg, raloxifene 60 mg, calcium carbonate 600 mg, penicillin V 500 mg (for secondary prophylaxis after recurrent erysipelas) per day. Her vital signs included height 156 cm, weight 65 kg, temperature 36.7^{o}C, blood pressure 132/64 mmHg while standing, and heart rate 77 bpm. A grade 3/6 systolic ejection murmur and a grade 2/4 regurgitant murmur were audible over the aortic area. The jugular veins were not engorged and there was no hepato-jugular reflux.

Wide regions of bright red inflammation were noticed in the distal areas of the calves and dorsa of the feet, with distinct demarcation between involved and normal skin. A number of reticular veins were seen adjacent to the maleoli, but no varices were apparent. Two shallow ulcers were noticed in the antero-lateral aspect of the left calf, 2 x 2 cm in diameter, as well as several tiny exulcerations covered with a sero-sanguinolent exudate. The toe web spaces contained a macerated scale suggesting tinea pedis infection (Figure 2A). The pulsations of the tibialis posterior and dorsalis pedis arteries were normal. In the standing position, the skin color changed almost instantaneously becoming cyanotic and a substantial swelling of the distal part of the calves occurred within minutes (Figure 2B).

Laboratory studies revealed white blood cell count 11.000/mm^3 with 68% neutrophils and C reactive protein 88 mg/L. The chest X rays showed an enlarged cardiac silhouette. The ankle brachial indices were 1 and 1.1, respectively. Venous Doppler ultrasonography showed reflux in the deep venous system below the sapheno-femoral junction in the femoral vein as well as in the great saphenous vein. Since varicosities were not present in the calves, full examination of the small and great saphenous veins below the knee was not performed. Based on results of the ultrasonographic examination, the diagnosis of venous insufficiency was established. Treatment with oral ciprofloxacin was continued for 10 days, topical ZnO_2 was applied to the erythematous areas, compression bandages to the calves, antifungal paste to the interdigital spaces, and regular walking was recommended. The body temperature remained normal. There was slow and continual improvement of the calf erythema and the serous exudation came to an end.

In summary, this patient presented with an acute dermatitis resembling erysipelas on both calves, but without associated fever and systemic symptoms. At presentation, the working diagnosis was cellulitis caused probably by strains resistant to penicillin, since the disorder evolved while the patient was taking penicillin V prophylaxis. Isolation of pseudomonas aeruginosa from the base of the skin ulceration was the reason for ciprofloxacin treatment, initially empirically and later in agreement with antibiotic sensitivity. This case history raised several questions.



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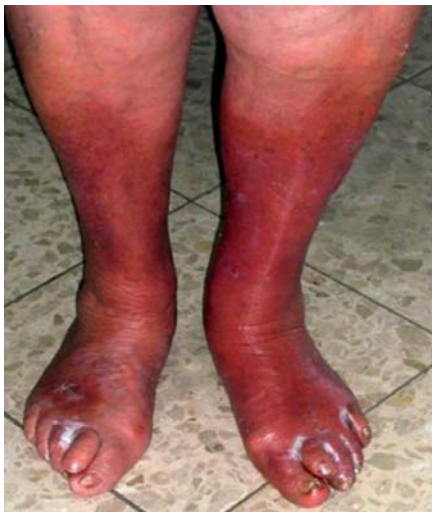

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Figure 2. Stasis dermatitis appearing as wide areas of bright red inflammation in the distal areas of the calves and dorsa of the feet, with distinct demarcation between involved and normal skin. *A.* Two shallow ulcers visible on the antero-lateral aspect of the left calf. *B*. On standing up the skin color changed to cyanotic.

First, what is the pertinence of surface microflora collected from leg wounds for diagnosing infection versus contamination? An ideal method of sampling the microflora of wounds has not been established and remains controversial [56,57]. It has been asserted that swabbing alone fails to provide information on the bacteria invading the deep tissue of the wounds [57]. In patients with cellulitis adjacent to a cutaneous ulcer, skin biopsy has yielded mostly staphylococci or streptococci, contrasting with the variety of bacteria identified upon swabbing the base of the wound; clinical improvement resulted from treatment directed against staphylococci or streptococci unrelated to antibiotic sensitivities of the superficial microflora that was sampled by swabbing the wound base [58]. Hence, assessment of chronic wounds for the presence of infection is a difficult task and the distinction between bacterial colonization and infection relies chiefly on clinical judgment [59]. In our patient, the growth

of proteus in the specimen obtained by swabbing the shallow skin ulceration may signify contamination, since the patient had neither fever, nor debries or purulent discharge. On the other hand the possibility of genuine infection could not be discarded.

Second, what is the patient's diagnosis if not erysipelas? Easily excluded were contact dermatitis, atopic dermatitis and xerosis [60]. Allergic contact dermatitis rarely occurs with modern wound dressings and is exceptional with ZnO_2 topical application [61-63]. 'Venous eczema' also called *chronic stasis dermatitis* is an itchy rash confined to the lower legs of patients with venous disease, a poorly demarcated, scaly eruption that responds well to topical corticosteroid treatment. Most patients with venous insufficiency do not develop venous eczema, which suggests that genetic or environmental factors may play a predisposing role. Our patient's dermatitis was clearly different from venous eczema. *Acute stasis dermatitis* is an appropriate consideration in our patient, occurring on the background of venous insufficiency that has been substantiated on venous ultrasound examination. Acute stasis dermatitis appears as a red, superficial, itchy plaque suddenly emerging on the lower leg. Weeping and crusts may appear. Skin biopsy of stasis dermatitis, although rarely indicated, shows an acute or subacute dermatitis. This acute process can easily be confused with an infectious cellulitis [64-66]. Even more, stasis dermatitis is often the first manifestation of venous insufficiency that has not been diagnosed previously and needs to be evaluated and treated [66]. Acute stasis dermatitis as the presenting feature of chronic venous insufficiency was the final diagnosis in our patient.

Acute stasis dermatitis responds to treatment with systemic antibiotics, wet compresses, and topical steroids [60]. Topical treatment has much in common with the treatment of other forms of acute eczematous dermatitis. Weeping lesions can be treated with wet-to-damp gauze dressings soaked with water or with a drying agent, such as aluminum acetate. Topical corticosteroids are frequently used for reducing inflammation and itching in acute flares; triamcinolone 0.1% ointment is generally effective. However, by using topical corticosteroids the patient may become more susceptible to infection. Open excoriations and erosions should be treated with a topical antibiotic, such as bacitracin. Superficial impetiginization should be treated with topical mupirocin or a systemic antibiotic [64]. The recently approved nonsteroidal calcineurin inhibitors tacrolimus and pimecrolimus may prove to be useful tools in the management of stasis dermatitis [67].

Third, what is the significance of instantaneous cyanosis and edema that occurred upon assuming the erect position? This is not a characteristic feature of erysipelas or cellulitis. Several possibilities that were considered in the differential diagnoses could easily be discarded. One of these is acrocyanosis, which is diagnosed clinically and is characterized by persistent cyanosis of the hands, feet, or face. The extremities often are cold and clammy and may exhibit some swelling. An other differential is erythromelalgia, a disorder very different from the features noticed in our patient, since erythromelalgia is characterized by episodic painful burning sensation, erythema and swelling in the extremities [60].

Could the pathophysiologic mechanisms underlying to acute stasis dermatitis explain the instantaneous cyanosis and edema upon assuming the erect position? As a rule, hyperemia of any cause (stasis dermatitis or erysipelas) is characterized by increased inflow of oxygenated blood, thereby resulting in erythema. In contradistinction, venous engorgement and stasis is associated with diminished flow in the capillary bed that is swollen with deoxygenated

venous blood – its clinical expression may be cyanosis. Acute stasis dermatitis, i.e. inflammation on the background of venous insufficiency, entails equally hyperemia and stasis. In chronic venous insufficiency the skin capillaries are engorged as demonstrated with orthogonal polarization spectral imaging; the capillary diameter, capillary bulk and functional capillary density are increased compared to controls; severity of the microcirculatory alterations correspond to the clinical severity of venous insufficiency [68].

The vasodilatory property of raloxifene has been described previously[69] and in our patient, the vasodilatory effect of raloxifene may have contributed to hyperemia [69]. The increased inflow to the calves (due to the conjoint effects of dermatitis, raloxifene and augmentation of arterial inflow by assuming the standing position) in addition to diminished outflow (due to venous insufficiency) may have resulted in a substantial engorgement of the microcirculation and explain the unusual clinical syndrome of instantaneous dependent cyanosis and edema. However, the proof to this hypothesis is lacking because plethysmography with and without proximal venous occlusion, with and without raloxifene administration, was not available.

Learning points:

- Chronic stasis dermatitis appears as a chronic, poorly demarcated, scaly, itchy rash occurring on the lower legs in patients with venous disease. It is clinically distinct from erysipelas.
- Acute stasis dermatitis appears as a red, superficial, itchy plaque emerging swiftly on the lower leg in patients with venous disease. This acute process can easily be confused with erysipelas or infectious cellulitis.
- Acute stasis dermatitis may be the first manifestation of an occult venous insufficiency. In such case, the diagnosis may be even more challenging.

Case 3 - stasis papillomatosis An 82-year-old woman was admitted with paroxysmal atrial fibrillation. She had a history of ischemic heart disease and stroke; coronary artery bypass graft was performed 8 years earlier. The patient's medical history included several episodes of erysipelas of the calves and a painless eruption that occurred on the calves during the preceding year, without fever, itching or pain. Her current medications were aspirin 100 mg, carvedilol 25 mg, simvastatin 20 mg and furosemide 40 mg per day. On physical examination, the temperature was 36.4^{o}C, the blood pressure 128/77 mmHg, the heart rate 62 bpm, respirations 20/min. Numerous erythematous papulae and superficial nodules were noticed over the calves, as well as an orange-peel edema and pasty induration in the distal 2/3 of the calves, but no varices or venectasia (Figure 3A and 3B). The ankle brachial index was 0.7 on the right and 0.6 on the left side. The white blood cells count was 5300/mm^3 and the C reactive protein was 8 mg/L. The patient's cardiac condition stabilized and she was discharged on the following day. The eruption on the calves was consistent with stasis papillomatosis.

Stasis papillomatosis is a condition usually found in chronically congested limbs; it may complicate lymphedema, chronic venous insufficiency, trauma, and recurrent erysipelas. Local dermal lymphostasis seems to be the common pathogenetic mechanism in spite of different etiologies [70,71]. The lesions vary from small to large plaques that consist of

aggregated brownish or pinkish papules with a smooth or hyperkeratotic surface. The lesions most frequently affect the dorsum of the foot, the toes, the extensor aspect of the lower leg, or the area surrounding a venous ulcer. The clinical significance and prognosis is derived from the primary disease.

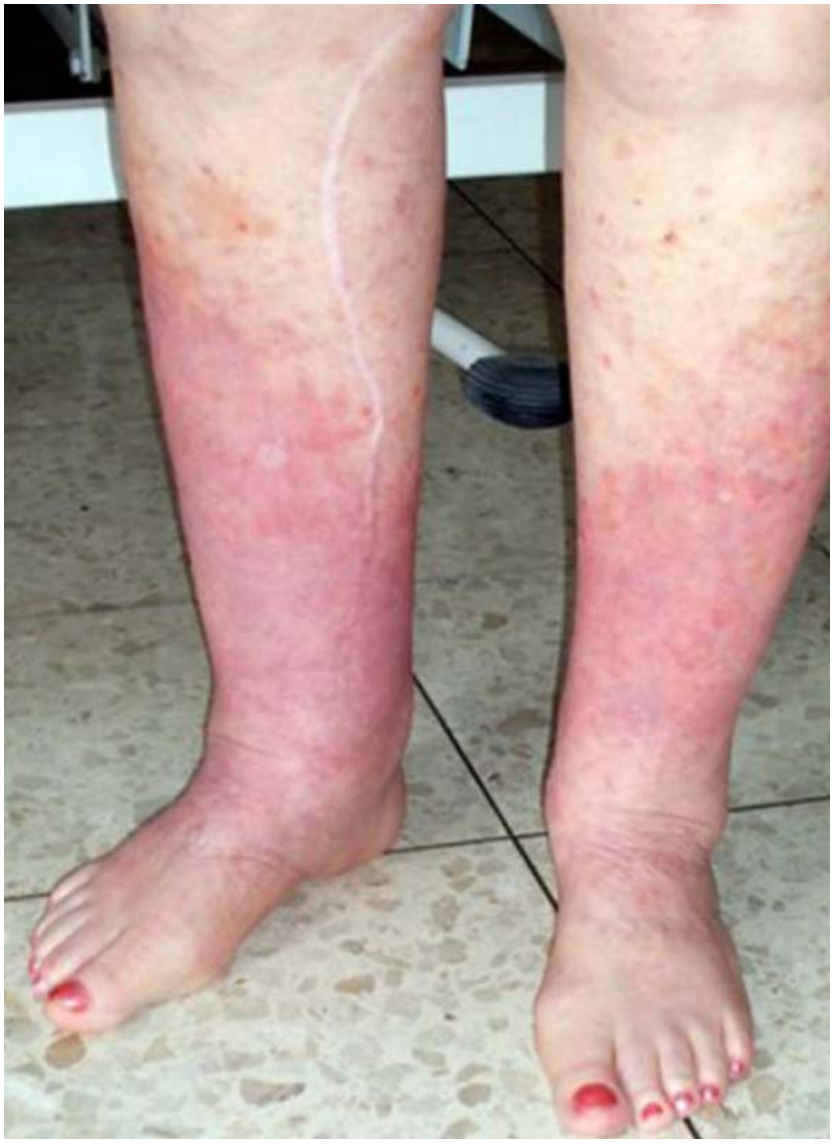

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Figure 3. (Continued).

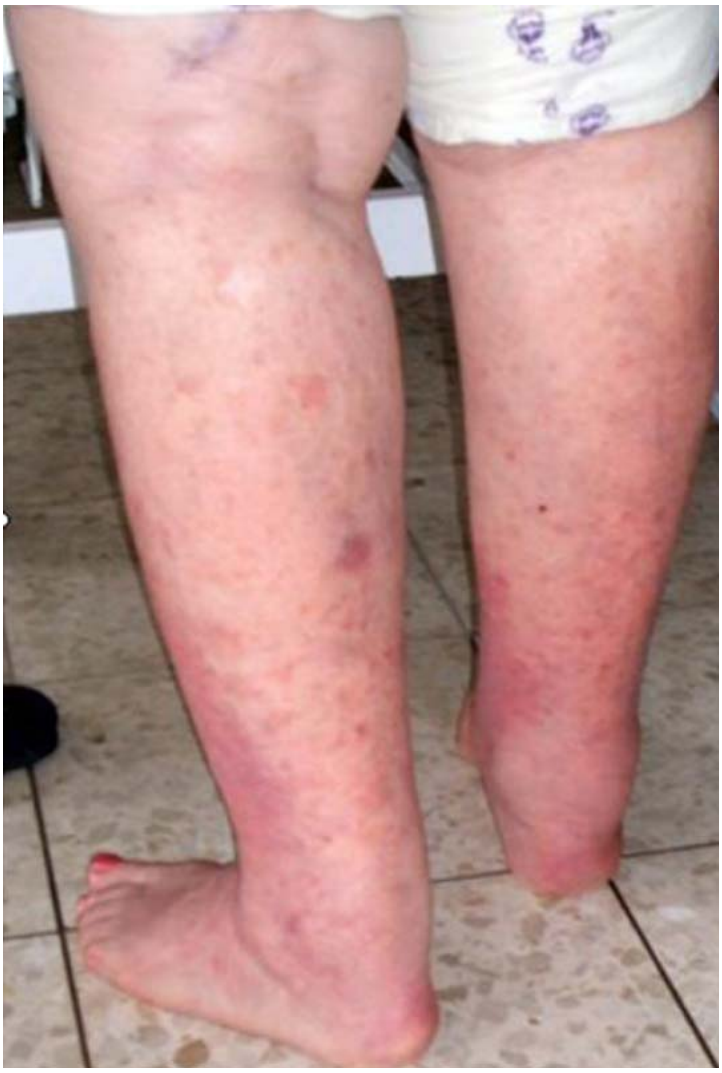

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Figure 3. Stasis papillomatosis.

Learning points:

- Stasis papillomatosis is characterized by small erythematous papulae or plaques involving the dorsum of the foot, the toes, the extensor aspect of the lower leg, or the area surrounding a venous ulcer.
- Stasis papillomatosis is usually not associated with systemic or local symptoms and is easily distinguished from erysipelas or stasis dermatitis.
- Treatment is directed toward the underlying cause, namely lymphedema, chronic venous insufficiency, trauma, and recurrent erysipelas.

Common disorders like erysipelas, cellulitis and stasis dermatitis are usually easy to recognize. However, atypical cases may confront the clinician with diagnostic problems. The complexity of apparently simple situations is illustrated in this chapter.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter VIII

Cutaneous Eruptions

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Most practitioners are familiar with the commonly encountered dermatoses in the elderly, but eruptions with atypical features may defy the clinician's expertise [1]. Further investigations and specialist referral may be indicated. The implicated problem solving may enhance our diagnostic skills.

Case 1 – paucivesicular herpes zoster An 87-year-old man was admitted to the geriatric ward after an episode of Campylobacter jejuni diarrhea. He was treated with ciprofloxacin 500 mg/day and the diarrhea and fever remitted but he continued to have a confusional state. Transferred to the geriatric ward, the maximum rectal temperature was 37.3°C. Routine laboratory tests showed normocytic anemia and moderate renal failure (hematocrit 34%, blood urea nitrogen 45 mg/dL, serum creatinine 1.6 mg/dL, estimated creatinine clearance (eCCT – MDRD) 31 mL/min. On the second week after his admission to our ward a vesicular eruption appeared on the patient's face, consisting of five tiny, shallow vesicles and subsequently crusts, confined to the antihelix of the right ear, the right malar area and the chin (Figure 1). The rash terminated exactly at the midline not expanding onto the left side of the face. Upon recognition that the vesicular eruption followed a dermatomal distribution, namely the area of the mandibular division of the right trigeminal nerve, a tentative diagnosis of herpes zoster was made. The content of a vesicle was aspirated for bacterial culture and acyclovir treatment was started intravenously. The dose of acyclovir was adjusted to the patients eCCT, i.e. 5 mg/kg intravenously twice daily. Measures of contact isolation were applied. The crusts felt off after a week and the eruption healed. The results of smears and cultures for bacteria were negative. The later course was complicated by other infections (see Chapter VI, Case 3).

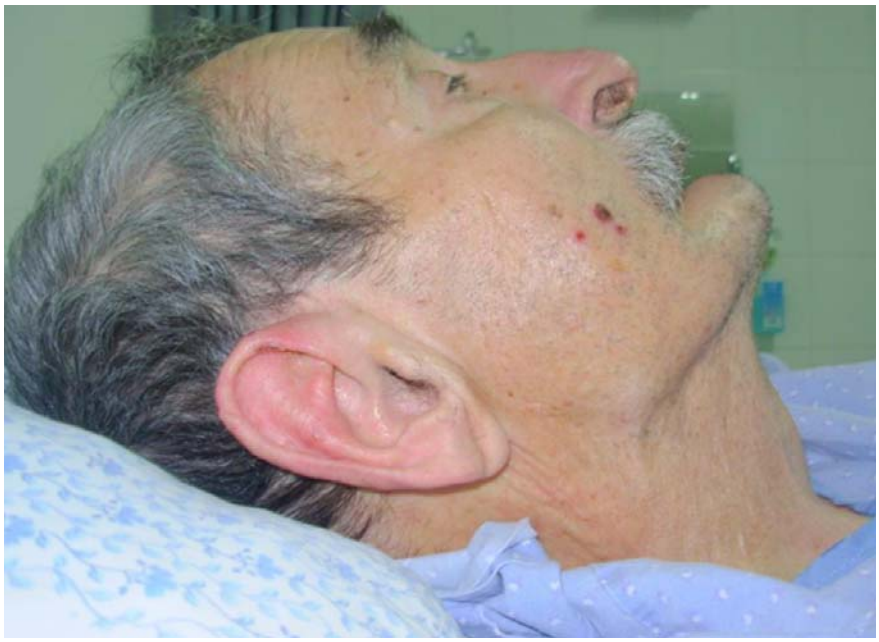


Figure 1. Paucivesicular herpes zoster confined to the mandibular area of the trigeminal nerve.

This case illustrates two exceptions to the common presentation of trigeminal herpes zoster: first, absence of neuralgic pain and, second, a paucivesicular eruption. The typical patient with herpes zoster presents a painful eruption of numerous grouped vesicles in a dermatomal distribution. The disease onset is with headache, fever and malaise, followed within a few days by a sensation of burning pain or itching in the affected dermatome. After another few days a number of hives appear in a dermatomal distribution, than the rash becomes vesicular.The vesicles have various sizes, a distinguishing characteristic from herpes simplex in which the vesicles are of uniform size. Subsequently, the serous content of the vesicles becomes cloudy or darkened, then form crusts. The crusts fall off within seven to ten days and the lesions heal, but scarring and discolored skin may remain [2].

If the rash has appeared, diagnosis only requires visual examination. Laboratory tests are generally not necessary (viral cultures and a Tzanck smear will confirm the diagnosis in patients with atypical presentation), since very few diseases produce a rash in a dermatomal pattern. A dermatomal distribution of the eruption is occasionally noticed in *herpes simplex* virus infection; though most commonly the herpes simplex eruption occurs in the oral, perioral and genital areas, it may occur in any site of the body and may also appear in a dermatomal distribution [3]. *Dermatitis herpetiformis* a rare, chronic skin disorder characterized by an intensely burning, pruritic, vesicular rash. It is strongly associated with gluten-sensitive enteropathy. The lesions are grouped, hence the name herpetiform. At first presentation, dermatitis herpetiformis may manifest with a few itchy papules or vesicles. At this stage the diagnosis may be difficult. In time the disease evolves into its classic presentation with grouped lesions symmetrically distributed on extensor surfaces of the elbows, knees, scalp, nuchal area, shoulder, and buttocks. There is a strong connection of dermatitis herpetiformis with HLA-B8, DR3. Gluten-sensitive enteropathy is a common

associated finding. A history of chronic diarrhea associated with a chronic pruritic, vesicular rash is highly suggestive of the diagnosis. The diagnosis is confirmed on skin biopsy by demonstrating IgA deposits along the subepidermal basement membrane in the dermal papillary tips [4]. *Cutaneous malignancy* may exceptionally occur in a dermatomal distribution and masquerade as herpes zoster [5,6]. A vaguely dermatomal distribution was reported in a case of *imatinib mesylate*-induced cutaneous eruption [7]. Keratotic lesions with histological features of *dyskeratotic acantholysis* may appear in a zosteriform distribution, but they are clearly different from herpes zoster [8].

The presence of neuralgic pain is another key-feature of herpes zoster. In a study of 550 patients with herpes zoster, mean age 66.7 years, with cranial segments predominantly involved, herpes-related pain was reported in 77% of patients. Herpes-related pain heralds the eruption and may persist after resolution of the eruption for months or possibly years [9]. Among clinical variants of herpes zoster, two extreme situations are rare: pain without herpetic eruption [10] and zosterian eruption without pain [11]. In our patient, the association of paucivesicular and painless dermatomal eruption is an uncommon forme fruste herpes zoster, but not a difficult diagnosis. The diagnosis was further substantiated by cure of the eruption on acyclovir treatment.

Learning points:

- Painless and paucivesicular herpes zoster is uncommon, but the diagnosis is not difficult based on the dermatomal distribution of the blisters.
- The first line treatment of herpes zoster is acyclovir 800 mg five times daily orally for 1 week or 5mg/kg by intravenous infusion over 1 hour, q8h (may be increased to 10 mg/kg in severe infection or in case of immunosuppression).
- Doses of acyclovir should be reduced in renal impairment according to creatinine clearance. When the CCT is between 25 and 50 mL/minute the interval between infusions may be increased to 12 hours, when eCCT is 10 to 25 mL/minute the interval between infusions may be increased to 24 hours [12].
- Direct renal tubular toxicity has been described with acyclovir treatment. Prevention of acyclovir deposition in the kidneys can be accomplished by infusing the drug slowly. Hemodialysis, which removes significant amounts of acyclovir (40% to 60%), may be indicated when severe renal failure ensues.

Case 2 – herpes zoster without vesicles An 88 year-old-woman presented with flank pain and a maculopapular eruption devoid of vesicles, that were confined to the area of distribution of the thoracic nerves T8-T10 (Figure 2). The diagnosis of atypical herpes zoster was advanced [13] and acyclovir treatment was administered. Ten days later, at the time of discharge from hospital, the eruption became faint but no vesicles had occurred.

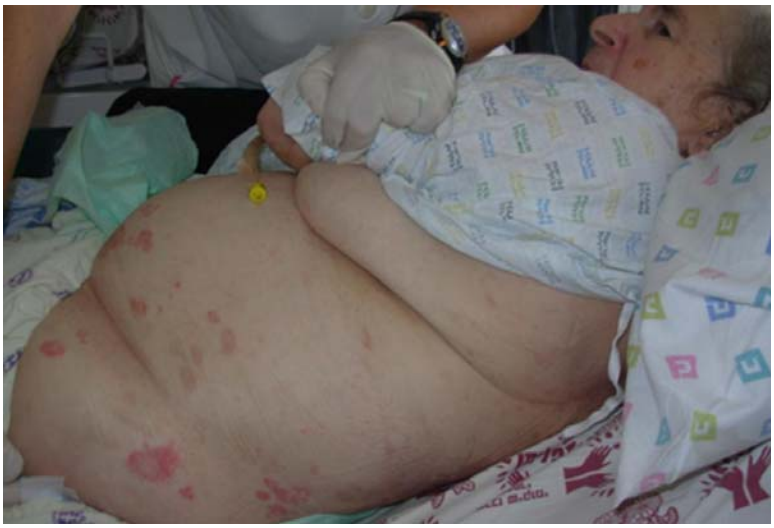


Figure 2. Herpes zoster featuring with macules, papules and plaques seven days after onset of the eruption.

Infections of the skin by herpes viruses do not always present themselves in the typical fashion. In a study of 75 patients diagnosed clinically as 'herpes zoster,' 'varicella' or 'herpes simplex', herpes zoster was misdiagnosed as herpes simplex in 30% of cases [14]. Biopsy of the cutaneous lesion may be useful. At low magnification, a superficial and deep perivascular, periadnexal, and interstitial mixed cellular infiltrate is revealed with lymphocytes admixed with a few eosinophils. Higher magnification shows focal epidermal necrosis, ballooning of the keratinocytes with pale eosinophilic cytoplasm, and margination of the nucleoplasm, suggesting early viral changes [14]. When macules and papules only are present, devoid of vesicles, the histopathologic correlates are superficial and deep infiltrate of lymphocytes that is dense perivascular and sparse interstitial with perivascular, periadnexal, and perineural arrangement, and with lymphocytes being present in epithelial structures accompanied by spongiosis, vacuolar changes, and necrotic keratinocytes, is typical of early zoster infection [9]. Orthokeratosis of the cornified layer and extravasated erythrocytes as well as edema of the papillary dermis are signs of the acuteness of the process. Extravasated erythrocytes also account for the purpuric color that may be encountered in macules and papules of early herpes virus infection [9].

Sometimes, on conventional microscopy, typical signs such as multinucleated epithelial cells or 'ghosts' of them are not encountered in the biopsy specimen – the so-called herpes incognito [15]. Polymerase chain reaction techniques may be used for confirmation and differential diagnosis of herpetic infections [9]. The diagnosis and differential diagnosis of herpes virus infections can be accurately established with the aid of the polymerase chain reaction, but this test is not yet available in large parts of the world [16]. Polymerase chain reaction on tissue specimen differentiates varicella-zoster virus from herpes simplex viruses type 1 and type 2 [14,17].

Learning points:

- Atypical variants of herpes zoster should be recognized, including a maculo-papular eruption devoid vesicles [1]), an atypical exanthem [14], a follicular variant [18], and neuralgic pain without cutaneous eruption [9].
- When vesicles are not present, skin biopsy specimens and polymerase chain reaction on the tissue may be helpful in the diagnosis.
- Bilateral symmetrical herpes zoster should not be confused with varicella [19-21].

A population-based study of the incidence of herpes zoster before zoster vaccine introduction showed that herpes zoster is a common disease and that the incidence has further increased in recent years. The frequency of herpes zoster increases with the age, most markedly in those aged 50 to 59 years. Among persons with herpes zoster, one in every four suffers from complications, including pain lasting longer than 30 days, ocular disease or motor neuropathies [22]. A vaccine to prevent herpes zoster was licensed for use in the United States in May 2007. The vaccine is indicated for routine administration to all immunocompetent adults age 60 years or older. The vaccine is contraindicated in all HIV-infected and other immunocompromised adults. The vaccine is administered once in a single dose. Whether booster doses will be needed is unknown [23].

Case 3 - herpetic whitlow An 89-year-old woman was admitted for recurrent E. coli urosepsis. She made an uneventful recovery on cefuroxime treatment. An indolent eruption was noticed on the patient's right hand, confined to the ventral aspect of the second and first phalanxes of the 2nd, 4th and 5th finger. The eruption consisted of crops of small vesicles, some of which were confluent (Figure 3). This eruption has been first observed by the patient's caregiver six weeks ago. The remainder of the skin, perianal area, oral mucosa, and gynecological examination were unremarkable. Herpetic whitlow was diagnosed and treated with topical acyclovir.

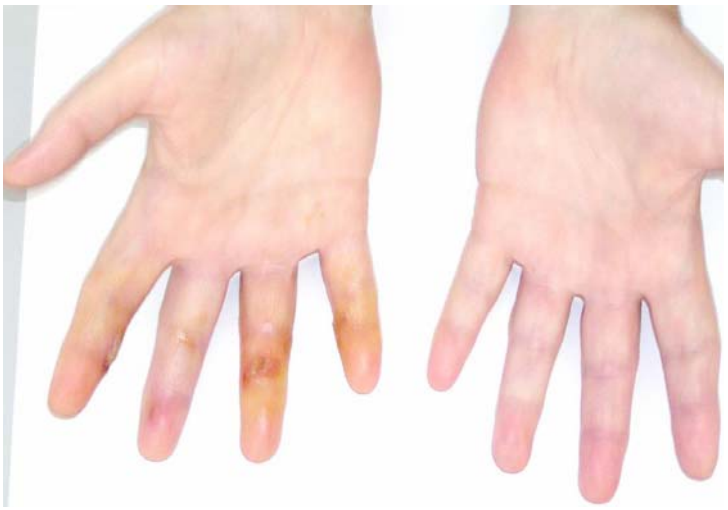


Figure 3. Digital whitlow.

Herpetic whitlow is a painful cutaneous infection that most commonly affects the distal phalanx of the fingers and occasionally the toes. It is caused by herpes simplex virus types 1 or 2. Herpetic whitlow occurs mainly in adults aged 20 to 30 years and children. Herpetic whitlow has been known mainly for infecting healthcare workers, often as the result of exposure of a digit on the dominant hand to a patient's active oral or genital lesions or to infected secretions in asymptomatic carriers [24].The implementation of universal precautions resulted in decline in the incidence of occupation-related cases. Herpetic whitlow may have a prodrome of burning, pruritus or tingling of the affected finger or the entire limb, followed by erythema, pain, and vesicle formation [24-27]. Indolent herpetic whitlow is the exception to the rule [28]. Herpetic whitlow should be differentiated from bacterial felon, paronychia and infiltration by malignancy [26,29]. The most rapid, inexpensive, and frequently used diagnostic tool is to take a cytological smear (Tzanck smear) from the base of a freshly opened vesicle. The collected specimen is examined for virally-induced cytopathological features by light microscopy. Although the Tzanck test confirms herpes simplex or herpes zoster infection as the etiology, it cannot differentiate between them. Herpetic whitlow is a self-limiting condition. Antiviral therapy may benefit patients with extensive disease. Management does not target viral eradication, but rather the prevention of transmission, suppression of recurrence and attenuation of clinical course. Herpetic infections of digits typically heal over 3 to 4 weeks but may recur [27]. Topical, oral, or intravenous antiviral agents may be used in the management of herpes simplex virus infections [25].

Case 4 – vesicular perioral eruption An 82-year-old woman with advanced dementia was admitted for the treatment of grade IV presacral pressure sores complicated with cellulitis and high fever. Her temperature was 39.2^{o}C, the blood pressure 118/79 mmHg and the heart rate 98 bpm. After surgical debridement of necrotic tissues, empirical treatment with ciprofloxacin and clindamycin was started. The temperature returned to normal after 3 days and the patient's general state improved. At this time an eruption appeared on the perioral skin (Figure 4), also involving the vermilion border of the upper lip. A few similar vesicles were noticed on the anterior chest wall. The content of two vesicles was aspirated for bacterial smears and revealed staphylococcus aureus. Cytological examination of the smear did not show inclusion bodies or multinucleated giant cells. Combined treatment with oral acyclovir and topical mupirocin was followed by regression of the eruption. The differential diagnosis in this case pertains to perioral eruptions.

Herpes labialis infection may appear on the lips, nose or in the surrounding areas as a painful blistering eruption, consistent of multiple clustered confluent vesicles and pustules. It is often associated with fever. The vesicles are uniform in size in contrast to herpes zoster vesicles which vary in size. The vesicles usually ulcerate or crust within 48 hours. Typically, herpes labialis tends to recur. Herpes simplex labialis is easy to diagnose based on the clinical presentation.

E*czema herpeticum* the association of two common conditions: atopic dermatitis and herpes simplex infection. The disease is most common in areas of active or recently healed atopic dermatitis, particularly the face, but normal skin can be involved. The disease in most cases is a primary herpes simplex virus infection. Approximately 10 days after exposure, numerous vesicles develop, become pustular, and umbilicate. High fever and adenopathy occur 2 to 3 days after the onset of vesiculation. The fever subsides in 4 to 5 days in

uncomplicated cases. Secondary staphylococcal infection commonly occurs. Management is difficult, particularly if the patient is immunocompromised. In doubtful instances, the Tzank smear may provide confirmatory evidence by revealing multinucleated giant cells, but the sensitivity of this test is not more than 60%. Treated with acyclovir or valacyclovir there is rapid clearing of the lesions [25,30].

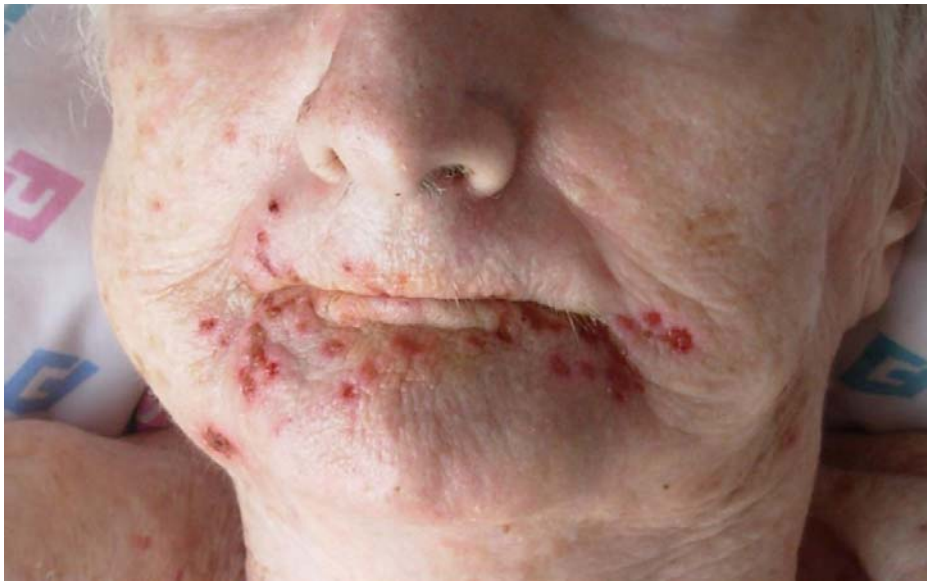


Figure 4. Perioral discrete vesicular eruption also involving the vermilion border of the lips.

Impetigo is a superficial skin infection generally secondary to *Staphylococcus aureus* and/or *Streptococcus* species [31]. Common presentations are bullous impetigo and nonbullous impetigo. Nonbullous impetigo begins as a single red macula or papula that quickly becomes a vesicle. Rupture of the vesicle produces an erosion, the contents of which dries to form honey-colored crust. Multiple lesions with golden yellow crusts are often found on the skin around the nose, mouth as well as the limbs. Bullous impetigo is characterized by rapidly enlarging vesicles growing to form bullae with contents that vary from clear to cloudy. There is subsequent collapse of the center of the bullae and a honey-colored crust may appear in the center. Constitutional symptoms are generally absent. Unroofing the lesions and Gram staining of the smear sampled from the base of the lesion reveals gram-positive cocci. Because Staphylococcus aureus commonly produces penicillinase, treatment with penicillin alone often fails. Penicillinase-resistant oral penicillins (such as dicloxacillin) or cephalosporins (cephalexin, cefadroxil) are very effective treatment. Topical mupirocin or fusidic acid are equally, or more effective than oral treatment for people with limited disease [32].

Perioral dermatitis is a common skin problem that mostly affects young women. It is a distinctive eruption that resembles acne. Papules and pustules on an erythematous or scaling base are confined to the chin and nasolabial folds, sparing a clear zone around the vermilion border of the lips. Similar and concomitant lesions are sometimes found around the nose, eyes, and on cheeks. There are varying degrees of involvement, some patients having only a

few pustules on the chin and nasolabial folds. The etiology is unknown, although many contributing factors have been implicated: fluorinated topical corticosteroids, subclinical irritant contact dermatitis, and overmoisturization of skin. Some dermatologists believe that it is a form of rosacea or sunlight-worsened seborrheic dermatitis. It may last a long time. It usually causes a little burning, stinging, not much itching. Perioral dematitis resolves with oral tetracycline (250 mg two to three times daily for several weeks) or erythromycin treatment [33].

In our patient, unroofing a vesicle revealed staphylococci, thus substantiating the clinical impression of impetigo. The confluent lesions on the vermilion border of the lip were consistent with herpes simplex infection, though cytological examination of specimens obtained from a second vesicle were unrewarding. Our tentative diagnosis was impetigo complicating labial herpes simplex. Cutaneous herpes simplex virus type I in association with Staphylococcus aureus has been described in the literature, particularly in infants [34]. Response to combined treatment brought significant improvement of our patient's eruption. However, two days after discharge to the nursing home the suffered a massive pulmonary aspiration and died.

Case 5 – impetigo A 78-year-old man presented with a vesicular eruption involving the volar aspect of the right thigh and calf. Though painless, the diagnosis of herpes zoster was suggested (Figure 5). The patient had recently completed a course of colistin sulfate treatment for urinary tract infection caused by carbapeneme-resistant Klebsiella pneumoniae. According to the patient's spouse, a number of blisters were already present a few days before antibiotic treatment was started. On physical examination, the patient's general condition was satisfactory, the temperature 36.8^{o}C, and the blood pressure 124/72 mmHg. In addition to the eruption localized on the right thigh and calf, described at referral, a few similar blisters were noticed on the contralateral calf and anterior chest wall. Unroofing two pustulae, with Gram stain, Tzank smear and culture of the aspirate were unrewarding. The diagnosis of impetigo was put forward, assuming that the cultures were negative due to prior antibiotic treatment. Topical treatment with mupirocin was applied and the eruption subsided after two weeks.

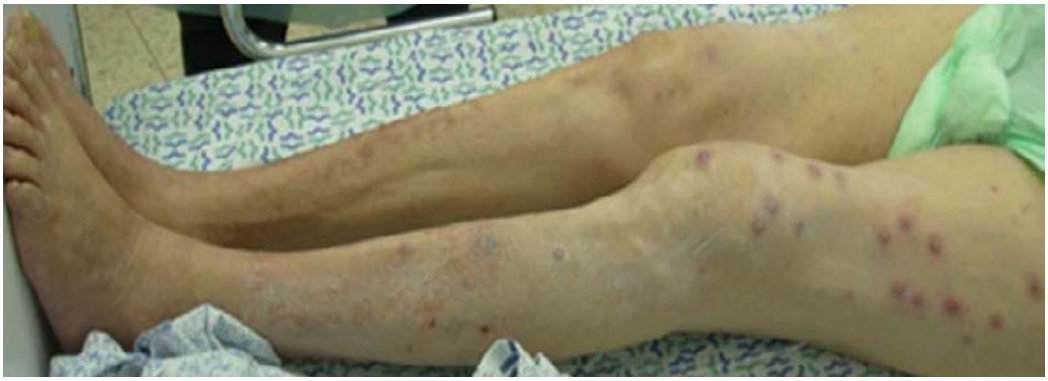


Figure 5. Vesicular eruption mainly but not exclusively confined to the distribution area of the right lumbar nerves L2-L3.

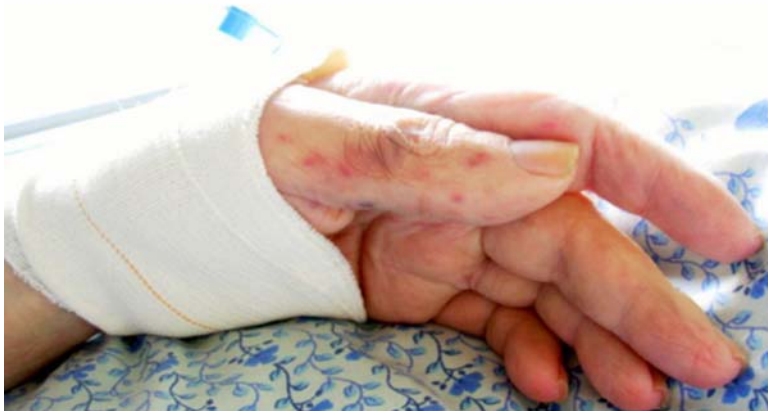
Learning points:

- Impetigo generally appears as 'honey-colored' scabs often found on the arms, legs or face.
- The diagnosis is straightforward and is supported by finding gram-positive cocci in the specimen sampled by scraping the base of a lesion.
- With atypical skin lesions, such smears have adequate sensitivity and specificity to guide early management decisions.
- In atypical cases the differential diagnosis should include herpes zoster, herpes simplex, tinea circinata and acute pustular psoriasis [35,36].
- When the vesicles of herpes simplex become turbid, they may look like impetigo.
- Localized acute pustular psoriasis may also be mistaken for impetigo.
- Impetigo can be efficiently treated with topical mupirocin or fusidic acid

Case 6 – eruption limited to soles and palms Palmoplantar involvement in the presence of a generalized rash may serve the clinician as a warning signal regarding possible life-threatening disorders [37,38]. On the other hand, the eruption may be limited solely to the palms and soles. The latter category include: Janeway's lesions in infective endocarditis, palmaoplantar erythrodysesthesia following chemotherapy, palmoplantar eccrine hidradenitis, dyshidrosis, palmoplantar pustulosis, palmoplantar hyperkeratosis associated with periodontal destruction, keratoderma blennorrhagicum, palmoplantar mycosis fungoides, and tripe palms [39-42]. Finally, eruptions beginning in the palms or soles may subsequently extend to other body areas.

The diagnostic puzzle regarding the etiology of an eruption restricted to a patient's palmo-plantar regions is presented. An 82-year-old man with Alzheimer dementia and arterial hypertension was referred with 39.6^0C fever that began earlier that morning. An eruption on the patient's soles had been noticed a few days before. The patient's regular medications were enalapril and aspirin. On examination, a grade IV pressure ulcer with surrounding cellulitis was found on the buttock. Pink-to-red maculae, 1 to 3 mm in size, were seen on both palmar and both plantar surfaces (Figure 6). The remainder of the skin and oral mucosa appeared normal. Ancillary tests showed raised C-reactive protein (225 mg/L) and white blood cells ($14.000/mm^3$). Blood and urine cultures were negative. Debridement of necrotic tissue and chloramphenicol treatment resulted in quick resolution of fever, but the palmo-plantar eruption remained unchanged along three weeks of the hospital stay. Serologic tests for rickettisia and later HIV and syphilis were unrewarding.

The palmo-plantar eruption pattern in this patient and the clinical course seemed not to match well known eruptions limited to the palms and soles. They were unlike *Janeway's lesions* which occur in infective endocarditis. Janeway's lesion may be purpuric, vasculitic or suppurative [39,43]. Tenderness is not associated with Janeway's lesions in distinction from Osler's nodes [44]. The patient's palmoplantar eruption also differed from *pustular eruptions of the hands* (the etiologies vary, including vasculitic, infectious and neutrophilic dermatoses) in as much the lesions were not pustular in type [40,45]. *Hand, foot, and mouth disease*,



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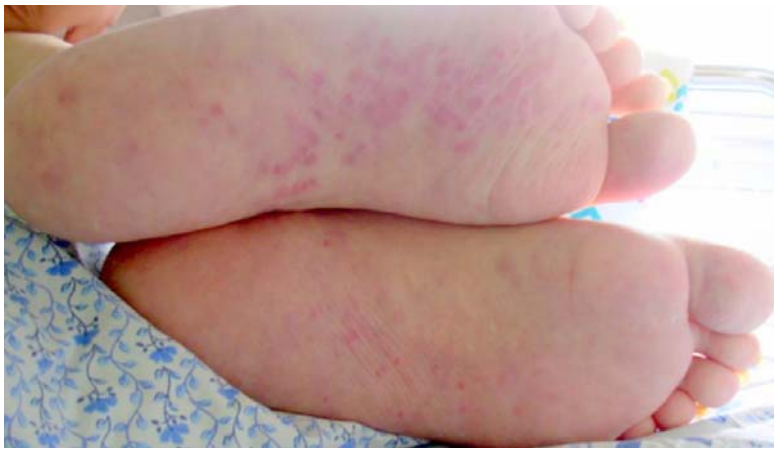

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Figure 6. Palmoplantar eruption. A. Macular eruption on fingers and palms. B. Macular plaques on the soles.

which has no relation to hoof-and-mouth disease in cattle, is a contagious enteroviral infection occurring primarily in children and characterized by a vesicular palmoplantar eruption. *Secondary syphilis* may cause red-brown, copper, or ham-colored macules or papulosquamous lesions on the soles of the feet. A painless papulosquamous eruption on the palms or soles in patients with gonorrhea called *keratoderma blennorrhagicum* may be associated with reactive arthritis [46]. *Mycosis fungoides palmaris et plantaris* is characterized by hyperkeratotic patches or plaques confined to the palms and soles; it is easily misdiagnosed because of resemblance with psoriasis, cutaneous inflammatory dermatoses, and dermatophytic infections. The diagnosis is established by skin biopsy. Mycosis fungoides may be difficult to differentiate histologically from other dermatoses in the early phases of the disease, but T-cell receptor gene rearrangement findings are diagnostic [47]. *Palmaoplantar erythrodysesthesia following chemotherapy* [41] is a complication of cytotoxic chemotherapy. It presents with paresthesia on hands and feet, followed within several days by painful erythema and edema; in severe cases bullae may form. Desquamation usually follows within weeks of resolution of the erythema. Skin biopsy characteristically

shows necrotic keratinocytes and vacuolar changes of the basal layer, papillary dermal edema, dilated blood vessels and perivascular lymphocytic infiltration. Many drugs have been associated with palmar–plantar erythrodysesthesia syndrome, including 5-fluorouracil, capecitabine, cytarabine, doxorubicin, epirubicin, docetaxel, vinorelbine tartrate and cyclophosphamide. Our patient's eruption was also easily distinguished from the common *dyshidrosis* and the rare paraneoplastic *tripe palms*.

The diagnosis remained enigmatic until results of skin biopsies were received. They showed the distinctive features of Kaposi sarcoma: labiryntic, thin walled, neovascular channels with irregular intraluminal projections and positive LANA immunostain of cells lining the atypical blood vessels. LANA immunostaining is a sensitive and specific marker of Kaposi sarcoma, useful in distinguishing Kaposi sarcoma from its mimickers [48,49]. In the present case, the cutaneous neovascularisation by dilated, irregular blood vessels, lined by LANA-positive endothelial cells, intermingled with lymphocytes and only a few spindle cells were characteristic of 'patch-stage' Kaposi sarcoma [49]. Two months later the plantar maculae enlarged and became clinically unmistakable Kaposi sarcoma type (Figure 7).

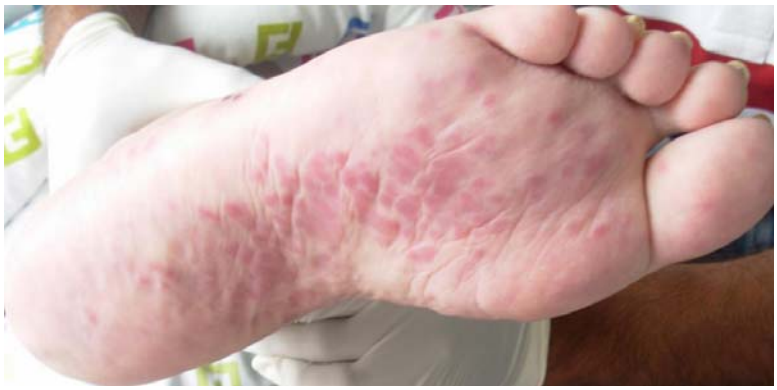

Figure 7. The macular plaques on the sole have much enlarged two months later (the same patient as in Figure 6).

Classical Kaposi sarcoma is a disease of older persons, beginning with multiple red to purple skin plaques or nodules primarily localized on the patients' arms or legs. The lesions slowly increase in size and spread to more proximal sites as well as distally to the palms and soles. The diagnosis is usually straightforward. However, presentation of Kaposi sarcoma with as a solitary palmo-plantar eruption is unusual [50]. For atypical presentations, as in the present case, a skin biopsy with immunostaining is the ultimate diagnostic means. In the present case, 'patch-stage' Kaposi sarcoma was diagnosed. It differs from the pseudotumoral and other palmoplantar presentations of Kaposi sarcoma [51,52].

In distinction from eruptions solely involving the palms and soles as in the present case, the palmoplantar eruption may be part of a generalized dermatosis. Several variants are well known. *Rickettisia* species may cause a generalized eruption also involving the palms and soles in the context of high fever and general symptoms. Immediate antibiotic treatment is an imperative [53]. *Drug reaction*s must be considered in any patient with a generalized maculopapular rash, especially if associated with palmoplantar involvement. Among

cutaneous reactions induced by drugs, Stevens-Johnson syndrome and toxic epidermal necrolysis are the more severe [54]. Erythema multiforme is a relatively common, acute, often recurrent inflammatory disease. Many factors have been implicated in the etiology of erythema multiforme including drugs, infections, physical agents and malignancies; in approximately 50% of cases no cause can be found. Dusky red, round maculopapules appear suddenly in a symmetric pattern on the back of the hands and feet and the extensor aspect of the forearms and legs. The diagnosis may not be suspected until the nonspecific early lesions evolve into target lesions during a 24- to 48-hour period. The trunk may be involved in more severe cases. Mucosal lesions may also occur, most commonly on the lips and oral mucosa.

A simplified diagnostic scheme of palmoplantar eruptions is presented in Figure 8.

Though practitioners are familiar with the more common skin eruptions, diagnostic problems may arise when a common disease masquerades under atypical features or in meeting a rare disorder. Such medical encounters are not uncommon in the acute geriatric ward.

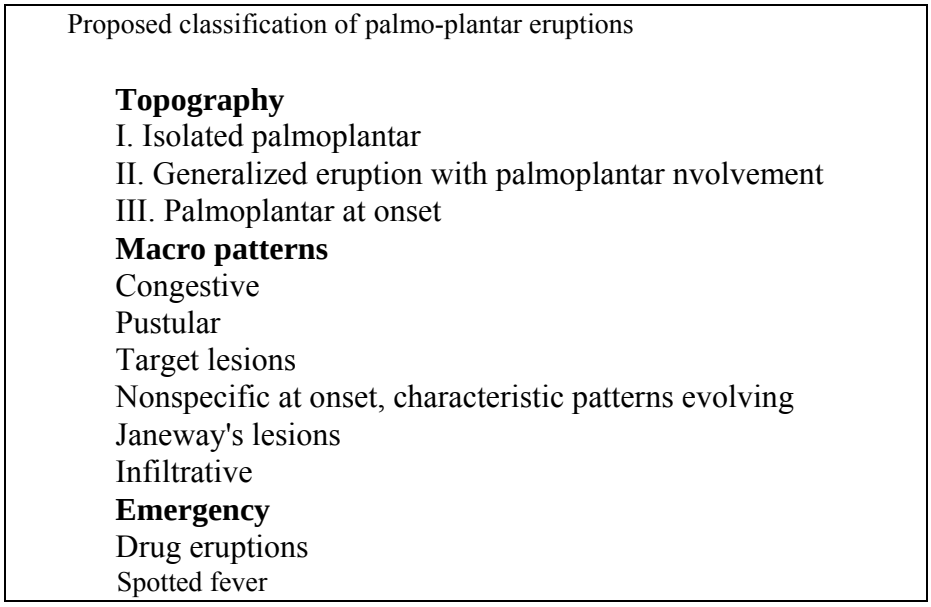

Figure 8. Proposed classification of palmoplantar eruptions.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter IX

Atypical Skin Ulcers

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It is hyaluronate which stabilizes the intercellular structures of the skin by forming a viscoelastic network in which collagen and elastin fibers are embedded. With aging, the hyaluronate in the extracellular matrix is diminished, leading to easy tearing and lacerations. The term 'dermatoporosis' has been proposed to embrace the different manifestations and implications of the skin atrophy, cutaneous fragility and insufficiency syndrome that is related to aging. The clinical manifestations of dermatoporosis usually become apparent after the age 60 years; more advanced dermatoporosis is perceived at 70 to 90 years of age. The dermatoporosis syndrome comprises: skin atrophy, senile purpura, stellate pseudoscars, frequent skin laceration, delayed wound healing and subcutaneous bleeding. On skin ultrasonography, the dermatoporotic skin is characterized by diminished thickness of the epidermis and dermis. Microscopic examination of skin biopsy specimen shows thinning of the epidermis and dermis the rete ridges being lost, as well as diminished collagen fibers, elastic fibers and mucin content in the dermis [1,2]. Dermatoporosis may be primarily related to the aging process, in which genetic factors may play a significant role [1], or may be secondary to chronic corticosteroid treatment either topical or following systemic administration. The primary and iatrogenic dermatoporosis have similar appearance on physical examination [3].

Skin atrophy is seen mainly in the areas exposed to sun, which are the posterior surfaces of the forearms and the pretibial zones. The atrophic skin becomes thin, transparent, with numerous wrinkles, and often purpura and pseudoscars. Senile purpura results from minimal trauma and in the absence of a coagulation disorder. Moreover, large hematomas may accrue after minimal trauma within the virtual space between the dermis and subcutaneous adipose tissue or between the subcutaneous adipose tissue and muscle fascia. Dermatoporosis may be complicated by *non-healing skin ulcers*. The mechanisms responsible for delayed wound healing of the dermatoporotic skin are decreased proliferative capacity of keratinocytes and

fibroblasts, abundant production of matrix metalloproteinases and secretion of cytokines which inhibit the dedifferentiation of keratinocytes [4,5]. Dermatoporosis should be treated to prevent pending complications [1,2].

I. Skin Ulcers in the Elderly – Four Common Etiologies

Four etiologies account for the large majority of skin ulcers in the elderly: ischemia, venous insufficiency, neuropathy and trauma [6-10].

Ulcers due to arterial insufficiency typically occur on the toes, heels or anterior shin. Arterial ulcers are round or punched-out and well demarcated; their base is covered by a yellow fibrin layer or by a necrotic eschar; tendons or bone may be exposed. Peripheral obstructive arterial disease is a common cause of ischemic ulcers; the patients complain of intermittent claudication and ischemic rest pain; chronic limb ischemia is characterized by hair loss, skin atrophy, nail dystrophy, and decreased or not palpable pulses; the ankle-brachial index (the ankle-to brachial systolic blood pressure ratio) is usually <0.7.

Venous ulcerations typically occur above the lateral or medial malleoli, but infection or trauma may localize the venous ulcers to other sites. Venous ulcers are usually shallow, have irregular borders, their base may be fibrinous or covered by granulation tissue. The patients usually have a history of venous insufficiency or deep venous thrombosis. On physical examination there are varicous veins, leg edema, hyperpigmentation, stasis dermatitis or lipodermatosclerosis. The ankle-brachial index is usually >0.9 (normal). It is often stated that clinical examination of the patient in good light provides nearly all the information necessary for the diagnosis of chronic venous insufficiency. However, the predictive value of clinical indicators of venous disease did not exceed 0.76 in one study [11]. To increase the accuracy of diagnosis of venous ulcer, clinical examination should be combined with non-invasive hemodynamic assessment of the venous circulation.

Neuropathic ulcers occur at pressure points, i.e. under metatarsal heads, over toe joints, under the heel, on the inner side of the first metatarsal head, and over the maleoli. The patients often complain of foot numbness or burning. Sensory neuropathy often leads to a loss of the protective sensation. Motor neuropathy leads to small muscle wasting and, consequently, to imbalance between flexors and extensors of the lower limb causing clawing of toes and prominence of the metatarsal heads that are thus exposed to pressure. Sympathetic autonomic neuropathy leads to dry, cracked, and fissured skin over the lower leg. Neuropathic ulcers are characterized by blister hemorrhage, necrosis, callus surrounding the wound, and exposure of underlying structures. Claw toes and Charcot joints may be associated findings. On monofilament testing for light touch sensitivity, the inability to perceive a 10 *g* of force applied by the monofilament is related to clinically significant large-fiber neuropathy [12]. The ankle brachial index is normal, unless neuropathy is associated with peripheral arterial insufficiency. Neuropathy may coexist with ischemia and act synergistically in increasing the risk of skin laceration, necrosis and defective wound heeling. Diabetics are prone to develop neuropathic ulcers. Rarer conditions responsible for

neuropathic ulcers include chronic alcoholism with malnutrition, leprosy, tabes dorsalis, spina bifida, and syringomyelia.

Among traumatic skin ulcers, pressure ulcers are defined as areas of localized damage to the skin and underlying tissue caused by pressure, shear, friction, or a combination of these [13]. The National Pressure Ulcer Advisory Panel in 1989 distinguishes four stages of pressure ulcers depending on the level of tissue breakdown: stage I characterized by nonblanching erythema of intact skin; stage II characterized by partial-thickness skin loss involving the epidermis, dermis, or both; stage III characterized by full-thickness skin loss involving damage or necrosis to subcutaneous tissue, which may extend down to underlying fascia; stage IV characterized by full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle or bone. Pressure ulcers usually develop on the lower half of the body, two thirds around the pelvis and a third on the lower limbs, with heel ulceration being most common. Risk factors for pressure ulceration are chronic disease, cerebrovascular accident, impaired nutrition, confinement to chair or bed, faecal incontinence, fractured neck of femur, altered consciousness, limited mobility, sensory impairment, severe chronic or terminal disease, vascular disease, malnutrition and dehydration [14].

The assessment and management of ischemic, venous, neuropathic ulcers and pressure sores has been reviewed in the recent literature and guidelines for treatment have been proposed [13-30]**.** Essentials are briefly reminded now.

Microbiology of Chronic Wounds

The significance of positive bacteriology smears and cultures differs when taken from neuropathic, venous or arterial leg ulcers. Only 22% of the venous ulcers with a positive smear developed a clinical infection; this contrasts to 70% of the arterial and diabetic ulcers where positive smears were indicative of clinical infection [22]. Therefore, wound smears should not be obtained routinely from patients with chronic venous ulcers. In 90% of diabetic skin ulcers that did not extend to the bone, the swab cultures identified all micro-organisms that were isolated from the deep tissue biopsy specimen [21]. Therefore, wound smears should be obtained routinely from patients with diabetic ulcers. Yet, preference is given to cultures obtained by curettage following debridement in order to identify the causative organisms in diabetic ulcers as well in other chronic wounds.

Basically, assessment of chronic wounds for the presence of infection is a difficult task. The distinction between bacterial colonization and infection cannot be founded on bacteriology alone, but relies very much on clinical judgment [20].

Likelihood of Osteomyelitis Adjacent to a Chronic Wound

The likelihood of osteomyelitis in a diabetic patient presenting a lower extremity ulcer can be estimated based on three criteria [25]. First, an ulcer area larger than 2 cm^2 indicates a 56% likelihood of osteomyelitis. Second, a positive probe-to-bone test indicates osteomyelitis with 53% probability. The probe-to-bone test is performed with a sterile, blunt, stainless steel

probe. The examiner gently probes the wound for the presence of a rock-hard structure at the wound base. A 'positive probe-to-bone result' indicates that the necrotic process probably involves the bone. Third, an ESR greater than 70 mm/h is associated with a 66% probability of osteomyelitis. Most clinicians believe that the presence of these 3 variables together would make the diagnosis of osteomyelitis certain and would treat as osteomyelitis [25].

Other clinicians might choose to order an MRI examination. A positive MRI result in combination with any one of the three clinical variables increases the probability of osteomyelitis to greater than 80%. On the other hand, the body temperature, ulcer inflammation, white blood cell count, and swab culture do not appear to be helpful in establishing the diagnosis of osteomyelitis in patients with diabetes and a lower extremity ulcer.

Prevention of Pressure Ulcers

Although a number of randomized controlled trials have evaluated preventive strategies for pressure ulcers, many of them had important methodological limitations [15]. Frequent change in body position is a mainstay in pressure ulcer prevention protocols, but there is insufficient evidence to recommend specific turning regimens for patients with impaired mobility [13,15]. Current practice requires that any individual at risk for developing pressure ulcers should be repositioned when lying in the bed at least every 2 hours; for patients who are in a chair repositioning should be done every hour. Pressure-relieving mattresses are classified into three groups, and patients must meet clinical criteria before reimbursement is provided: group 1 (static overlays and replacement mattresses); group 2 (low-air-loss beds, alternating pressure, and powered or nonpowered overlays or mattresses); and group 3 (air-fluidized beds). Most pressure-relieving mattresses do not decrease pressure below capillary closing pressure of 32 mm Hg; therefore patients need repositioning every 2 hours. The only true pressure-relieving surface is the air-fluidized bed, which is used for patients after flap surgeries and for patients who have no turning surfaces. In sitting position, there are specialty cushions that also reduce pressure and help to decrease the risk of pressure ulcers.

Treatment of Pressure Ulcers [13-15,31,32]

Making an accurate bacteriologic diagnosis of pressure ulcers is difficult, since every wound is contaminated by bacteria but not all wounds are infected. Swabbing a pressure ulcer often yields organisms that are colonizers and not actually causes of infection. It may be most appropriate to aspirate material from the margin or base of the pressure ulcer, directing the needle through intact skin or take a tissue biopsy. 'Critical colonization' is defined by bacterial load exceeding 1×10^5 colonies/g of tissue. Critical colonization affects the body's ability to heal and it becomes necessary to treat as infection. Clinical signs of infection are increased drainage, odor, surrounding erythema, pain, warmth, or simply a wound that has failed to improve despite adequate removal of necrotic tissue and maintenance of a moist wound environment. The time frame is usually a lack of progression after 14 days of therapy.

A consensus panel recommended the following wound dressings for the management of chronic wounds: in the debridement stage - hydrogels; for hemorrhagic wounds - alginates; for malodorous wounds - activated charcoal; in the granulation stage - foam and low-adherence dressings; in the epithelialization stage - hydrocolloid and low-adherence dressings [31]. Topical therapies for infected wounds include silver dressings, cadexomer iodine, hydrogen peroxide, povidone-iodine, diluted sodium hypochlorite solution, and chlorpactin. None of these treatments should be used longer than 14 days, because they can be toxic to healthy tissues. Topical antimicrobial agents have not been shown to be effective.

There is no need to treat a pressure ulcer with systemic antibiotics unless there are signs of adjacent cellulitis or osteomyelitis. Pressure ulcer–associated cellulitis, osteomyelitis, or bacteremia are usually caused by *P. mirabilis, S. aureus,* or *B. fragilis*. In general, any regimen that is active against the majority of organisms that are usually causal is appropriate. Although a 10- to 14-day course is commonly prescribed, there is no evidence based data to support this recommendation. A chronic, indolent, non-healing wound may reflect the development of underlying osteomyelitis, the flora of which is often Gram negative or anaerobic. Antibiotics are often started empirically. Osteomyelitis requires a more extended course of therapy. In patients with nutritional impairments, dietary supplements may be beneficial. Rarely, amyloidosis or malignancy may arise as a result of chronic pressure ulceration.

Treatment of Venous Ulcers [19]

Venous ulcer healing is facilitated by applying adequate compression to the lower extremity. The use of a class 3 high-compression therapy (three layer or four layer, low stretch or paste-containing bandages, e.g., Unna's boot) is indicated in the treatment of venous ulcers. The degree of compression must be modified when mixed venous/arterial disease is diagnosed on diagnostic work-up. The ankle brachial index is an important factor to consider in determining compression appropriateness. The type of dressing applied beneath compression has not been shown to affect ulcer healing [16,17]. Necrotic or devitalized tissue (tissue that is laden with bacteria) should be removed. If infection is suspected in a debrided ulcer, or if epithelialization from the margin is not progressing within 2 weeks of debridement and compression therapy, cultures should be performed on aerobic and anaerobic media by tissue biopsy or by a validated quantitative swab technique. **A**ntibacterial preparations should only be used in cases of defined infection and not for bacterial colonization [23]. Topically applied antimicrobials can be effective. For ulcers with $\geq 1 \times 10^6$ colony forming units/g of tissue or any tissue level of beta hemolytic streptococci following adequate debridement, topical antimicrobial therapy in indicated to decrease the bacterial level. Cellulitis surrounding the venous ulcer should be treated with systemic gram-positive bactericidal antibiotics.

Superficial venous surgery is associated with similar rates of ulcer healing to compression alone, but with less recurrence. The effect of deep venous insufficiency on the efficacy of surgery is unclear [18]. A significant proportion of patients are unsuitable for

surgical treatment. Growth factors, grafting, biologic skin substitutes, dressings, and oral medication have differing levels of evidence supporting their use [33].

Leg ulcers that worsen in size and symptoms despite treatment, or do not show any improvement over four weeks of treatment, should raise suspicion that the ulcer etiology is not venous in origin or that the therapy needs to be re-evaluated. At this point, specific cultures for mycobacteria and/or fungi are useful, as well as biopsies for histology.

Treatment of Diabetic Foot Ulcers [34]

Local treatment of the ulcer consists of repeated debridement and dressing, though the evidence of benefit of surgical debridement is not strong. Two studies reported a significant benefit of debridement with larvae. Complete excision of plantar neuropathic ulcers is associated with faster wound healing and with fewer recurrences. Some evidence was found to support hydrogels as desloughing agents. Systemic hyperbaric oxygen may be beneficial and decrease the need for major amputations; there are sufficient data to justify its use especially when revascularization is not possible [34,35]. The benefit of topically administered hyperbaric oxygen is not established. Whether topical negative pressure may promote healing of post-operative wounds is subject to controversy [36,37]. There is currently little evidence to suggest that growth factors and other agents modulating aspects of wound biology should be adopted in routine practice. Bioengineered skin products and skin grafts are widely used in some institutions, but their benefit has not been clearly established.

II. Other Etiologies of Skin Ulcers

In addition to the above described and frequently met skin ulcers, a variety of uncommon or rare etiologies should be considered in the differential diagnosis [30,38-44], as follows:

A. Ischemic ulcers may complicate the course of thrombangiitis obliterans, vasculitis (in particular microscopical variant polyangiitis nodosa, cryoglobuninemia, rheumatoid arthritis, Wegener's granulomatosis, systemic lupus erythematosus, nodular vasculitis), cholesterol embolism, antiphospholipid antibody syndrome, and calciphylaxis.

B. Hematological disorders: sickle cell anemia, warfarin-induced skin necrosis, heparin-induced thrombocytopenia, disseminated intravascular coagulation, essential thrombocythemia, therapy with hydroxyurea.

C. Trauma: burns, cold, factitial, stings, bites, skin aging.

D. Metabolic disorders: diabetes mellitus (necrobiosis lipoidica diabeticorum), gout.

E. Infections: ecthyma gangrenosum, furuncle, mycobacteria (Burundi ulcer caused by Mycobacterium ulcerans, erythema induratum Bazin caused by Mycobacterium tuberculosis), septic emboli, cutaneous leishmaniasis, cutaneous antrax, syphilis, leprosy, fungal infection (trichophytin granuloma, Cryptococcus neofomans, Coccidioides immitis).

F. Neoplasia: cutaneous T cell lymphoma, basal cell carcinoma, metastatic tumors, Kaposi sarcoma, squamous cell carcinoma, Merkel cell tumor, malignant transformation of a benign ulcer or scar ('Marjolin's ulcer').

G. Panniculitis: Weber Christian disease, pancreatic fat necrosis, alpha1-antitripsin deficiency.

H. Neutrophilic dermatoses: pyoderma gangrenosum, Sweet's syndrome.

Chronic leg ulceration is often met in patients during a hospital admission for various causes. Regardless of cause, hospital admission represents an opportunity for full examination of ulcers and further investigations or specialist referral if needed. Knowledge of different patterns of skin ulcers is important, to alert physicians to atypical appearances and lead to appropriate investigations and treatment [44-46]. Making a definite diagnosis is important for tailoring the treatment: corticosteroids for pyoderma gangrenosum or idiopathic vasculitides, antiviral treatment for hepatitis C virus-associated mixed cryoglobulinemia, antimicrobial or antifungal agents for specific infections, treatments for metabolic, hematological and neoplastic disorders.

III. Case History

The diagnosis may indeed be challenging, as illustrated in the following case history.

Case 1 – echymoses, crusts and skin ulcer A 72-yr-old woman has been suffering from progressive disability due to heart failure and chronic obstructive pulmonary disease. A recent exacerbation with pulmonary edema and atrial fibrillation with fast ventricular response was the cause of her admission to the medical ward. She was treated with furosemide, enalapril, pravastatin, verapamil, alopurinol and warfarin. A course of prednisone was instituted for exacerbation of chronic obstructive pulmonary disease, initially 40 mg/day than tapered to 20 mg/day; ciprofloxacin was added. On echocardiography, there were findings consistent severe pulmonary hypertension, mild aortic regurgitation, mild mitral stenosis and regurgitation, the left atrium diameter was 48 mm, and the left ventricular contractility was preserved. The patient had recently discontinued smoking. She was dwelling in the community, not being severely limited in activities of daily living.

Ten days later the patient was transferred to our geriatric ward for aftercare and rehabilitation. At this time she was receiving furosemide 120 mg, enalapril 20 mg, pravastatin 20 mg, verapamil 120 mg, alopurinol 100 mg, prednisone 20 mg, warfarin 2.5 mg, and ciprofloxacin 1 g/day. On physical examination the patient was confused, the bodily temperature was 36.8^{o}C, the blood pressure 120/72 mmHg, the heart rate 86 bpm, the respiratory rate 32 /min, the arterial oxygen saturation was 76% while breathing ambient air 93% on nasal oxygen mask. The jugular veins were engorged. The thorax showed barrel type deformity. Dry crackles were perceived over the lower half of the lung fields and a grade 4/6 systolic murmur at the cardiac apex and aortic foci. The skin in the distal area on the calves showed a mix of brown and violet shades; in the hyperpigmented areas the skin and subcutaneous tissues were indurated. Fourteen shallow skin lesions were counted, spreading over the distal part of the left thigh and left calf; these lesions measured 0.5 – 1 cm in diameter, were well demarcated, roundish, with slightly irregular borders; the lesions were covered by brownish crusts of apparently different ages. Laboratory tests were remarkable for C reactive protein 30 mg/L, serum creatinine 1.6 mg/dL, albumin 3.3 g/L, PT-INR 2.4, activated partial prothrombin time 32 seconds. Results of the blood cell count, liver function

tests and urinalysis were within the normal range. Chest X-rays showed an alveolar infiltrate confined to the lower lobe of the left lung.

The patient's previous medications were continued except for ciprofloxacine that was replaced by piperacilline-tazobactam 4.5g x3/day intravenously, and oxygen administered continuously by nasal mask. The disease course was complicated by a succession of events: delirium, that remitted after tapering the dose of prednisone to 5 mg/day; watery diarrhea clostridium toxin negative, which remitted on oral metronidazol treatment; a difficult to achieve warfarin therapeutic goal (PT-INR was in the range 1.3 to 1.7); and two echymoses emerging on the extensor aspect of the patient's left forearm, which subsequently became hemorrhagic blisters, expanding over one week time.

The larger of the two blisters reached 5 cm in diameter, had peripheral red borders and a violaceous liquid center. The nature of these skin lesions, blisters as well as areas covered by crusts, was unclear; a dermatologist consultant recommended that lesional skin biopsies be taken. Skin punch biopsies were obtained from the peripheral rim of the larger lesion. The content of the blister was aspirated and grew methicillin-resistant Staphylococcus aureus. Treatment with vancomycin was administered intravenously and hydrogel dressings were applied locally. A few days later, the lesion had transformed into a well demarcated ulcer with violaceous undermined borders and a clean basis (Figure 1). The skin biopsy showed an uncharacteristic mixed cellular infiltrate in the epidermis, dermis and subcutaneous layers.

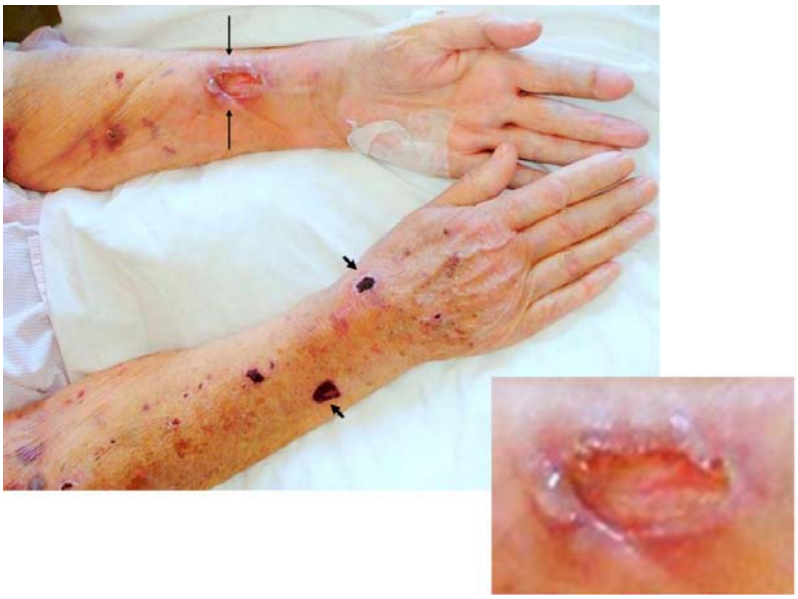

Figure 1. A skin ulcer is seen on the volar aspect of the left forearm (thin arrows). A magnification of the ulcerated area is shown in the inset. About 10 cm proximal to the ulcer there is a scaling crust surrounded by echymosis. The latter two lesions represent different outcomes of hemorrhagic blisters, which preceded by 7-10 days to the present findings. Numerous small lesions covered by brownish-violet crusts are seen on the dorsal aspect of the right forearm (thick arrows).

No granulomas or intracellular microbiota were seen. Several small lesions had appeared on the patient's forearms, covered by a brownish crust. Similar lesions, but at different phases of

evolution, some covered by crusts and others partially or completely epithelized, were seen on the thighs. The skin on the chest and abdomen was not involved. There was neither purpura nor evidence of mucosal bleeding. The patient's body temperature remained normal throughout her stay in our ward. Results of ancillary laboratory tests remained essentially unchanged. Antinuclear antibodies, C3 and C4 complement fractions, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, antiphospholipid antibodies, lupus anticoagulant, immune globulins IgG, IgA and IgM were unremarkable.

The differential diagnosis of the patient's skin lesions addressed several dermatologic disorders as well as cutaneous manifestations of systemic diseases and iatrogenic effects of corticosteroids and warfarin treatment. A 'pattern diagnosis' was attempted based on the appearance of the smaller skin lesions (that went through evolutionary stages of shallow skin necrosis covered by a crust) and the larger lesion (that went through evolutionary stages of a hemorrhagic blister to deep skin ulcer). The latter lesion was reminiscent of pyoderma gangrenosum.

Pyoderma Gangrenosum

The two primary variants of pyoderma gangrenosum are the classic ulcerative form usually occurring on the legs, and the more superficial variant known as atypical pyoderma gangrenosum that often occurs on the hands. Pyoderma gangrenosum may occur as a primary disorder or in association with another disorder, most often ulcerative colitis, regional enteritis, leukemia, preleukemic states or monoclonal gammopathies [48,49]. In addition to involvement of the skin, other organ systems may be affected in pyoderma gangrenosum by sterile neutrophilic micro-abscesses, which may localize to the lungs, heart, central nervous system, gastrointestinal tract, eyes, liver, spleen, bones or lymph nodes. Systemic manifestations are seen in 50% of patients with pyoderma gangrenosum; they can occur prior to, concurrently or following the cutaneous manifestations of the disease.

Patients with pyoderma gangrenosum usually describe the initial lesion as a small, red papule or pustule changing into a larger ulcerative lesion. Lesions may occur singly or in groups, most commonly on the lower limbs, although they may appear anywhere on the body. The lesions have a liquefying centre without eschar formation, purple undermining borders, which may be covered by hemorrhagic blisters. Pathergy, the phenomenon whereby lesions of a disease can be induced at sites of skin trauma, occurs in up to 50% of patients [48]. Pain is a frequent complaint of patients with pyoderma gangrenosum (pain was not present in our patient).

The histopathologic findings in pyoderma gangrenosum are not specific. Nevertheless, taking a biopsy is recommended in almost all affected patients because its usefulness in excluding other diseases. Microscopic features of pyoderma gangrenosum are massive neutrophilic infiltration associated with hemorrhage and necrosis of the overlying epidermis. Neutrophils may be observed around and within the vessel walls but the full picture of vasculitis is usually absent. The microscopical findings may simulate an abscess or cellulitis. In early disease, a mixed cellular infiltrate may be present [48]. In view of the nonspecific features on histological examination, the diagnosis of pyoderma gangrenosum rests on

clinical and pathologic features and also on exclusion of various conditions that may cause skin ulcers [48].

Therapy of pyoderma gangrenosum is based on corticosteroids and immunosuppressants. The smaller early lesions may be treated with intra-lesional injection of triamcinolone. Administration of systemic corticosteroids is recommended for larger active or fully evolved lesions. Prednisone 40 to 80 mg daily is required for initial control of the disease, followed by later tapering of the dosage. Pyoderma gangrenosum patients required a mean 11.5 +/- 11.1 months of treatment to achieve remission compared with 9.0 +/- 13.7 months for patients with atypical pyoderma gangrenosum [48]. Wound dressings are useful to minimize pain and the risk of secondary infection. The application of topical antibacterials is not recommended, but systemic antibacterial therapy is mandatory when infection is present. Recurrences are frequent after treatment termination [49-51].

Overall, the appearance of the patient's larger lesion was consistent with the superficial variant of pyoderma gangrenosum known as atypical pyoderma gangrenosum, provided all other etiologies of skin ulceration could be excluded. The numerous minute lesions on the patient's extremities but sparing the trunk could be explained as manifestations of pathergy. There were, however, several inconsistencies with this diagnosis. First, the skin lesions had appeared while the patient was receiving prednisone, initially 40 mg and later 20 mg/day. The initial presentation of pyoderma gangrenosum under pharmacologic dose prednisone treatment is uncommon. Later in the course of hospitalization, under the impression that prednisone might be the cause of the patient's confusional state, the dose was tapered to 5 mg/day. The delirium remitted and at the same time the skin lesions improved. The relatively fast improvement under physiological doses of corticosteroid administration is also uncharacteristic for pyoderma gangrenosum. Pyoderma gangrenosum being a diagnosis by exclusion, other entities were listed in the differential diagnosis.

Easily excluded based on clinical findings, histology and results of laboratory tests was a spectrum of ischemic ulcers, vasculitides, infectious ulcers (ecthyma gangrenosum, furuncle, mycobacterial and fungal ulcers), and ulcerated neoplasms.

Dissecting hematoma of the skin is a complication due to mechanical fragility of the aged skin. It occurs predominantly in the lower extremities of elderly patients suffering from skin aging (dermatoporosis). There is a female predisposition to dermatoporosis in general and dissecting hematoma of the skin in particular [2] Corticosteroids may predispose to dermatoporosis or aggravate preexisting dermatoporosis [1,2]. Dissecting hematomas of the skin may be precipitated by anticoagulant or corticosteroid therapy, as our patient was receiving. Corticosteroids are known to regulate the expression of genes encoding collagens I, III, IV, V, decorin, elastin, matrix metalloproteinases 1, 2, 3, tenascin as well as tissue inhibitors of certain matrix metalloproteinases [3]. In the presence of dermatoporosis, minimal trauma can cause massive bleeding into the virtual space between the dermis and subcutaneous adipose tissue or the subcutaneous adipose layer and the muscle fascia. The evolving hematoma destroys the blood supply to the skin and causes necrosis. In such situation immediate surgical evacuation of the hematoma and necrotic tissues should be performed to avoid extensive skin damage. Large and deep excisions may be necessary. The re-epithelization of larger defective skin surfaces may then be achieved by vacuum-assisted

closure or autologous thin skin grafts. Dissecting hematomas result in long and costly hospital stays.

The final diagnosis in our patient was dermatoporosis and dissecting hematoma of the skin, predisposed by anticoagulant and corticosteroid treatment was. Three months later the ulcer as well as the minute skin lesions were healed.

Learning points:

- Atypical skin ulcers may pose challenging diagnostic problems.
- A spectrum of vasculopathies, infections affecting the skin, ulcerated neoplasms, panniculitis and neutrophilic dermatoses should be considered in the differential diagnosis.
- Atypical ischemic ulcerations of the extremity are often non-atherosclerotic in etiology, may involve the proximal segments, and can evolve despite palpable distal pulses.
- A high index of suspicion is required to recognize atypical pyoderma gangrenosum in an older adult.
- Among the clinical manifestations of skin aging, dissecting skin hematomas cause significant morbidity needing hospitalization and urgent surgical procedures.

Chronic leg ulceration is a common condition often present in patient admitted to the geriatric ward. Four etiologies are responsible for the large majority of skin ulcers in the elderly: trauma, ischemia, venous stasis and neuropathy. In a minority of cases, skin ulcers are manifestations of other diverse disease states. The above presented case history illustrates how important it is that physicians are aware of the different patterns of skin ulcers. Acute admissions are opportunities for detailed examination of ulcers in their clinical context, to consider further investigations and specialized treatment if needed.

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In: Challenges in Acute Geriatric Care
Editor: Jochanan E. Naschitz
ISBN: 978-1-60741-309-7

Chapter X

Acute Orthopedics

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Advances in medical and orthopedic care, good for most 60 to 70 year-old patients, may not suit well the octogenarian or nonagenarian patient. Effective therapies may differ between the old and the oldest subjects, and had to change accordingly. First, comorbidities such as cardiovascular diseases, chronic obstructive pulmonary disease, osteoporosis, renal failure, and denutrition become more prevalent at older ages. Consequently, poly-pharmacy is more prevalent in the old and oldest age groups, with possible deleterious consequences. Second, aging is characterized by diminished functional reserve of different organs (heart, kidneys), impaired homeostatic reactivity (blood pressure), altered tissue vitality (skin, bones) and diminished regenerative capacity (skin, bones). It is not the same to treat a woman with a plaster cast if her skin is turgid and with a thick hypodermis than to use the same cast in a 90 -year-old woman with a thin and friable skin. Bones also become brittle in the old and may not respond as well as before to usual treatments. Third, the multiple system decline associated with aging is often uneven, varying among different organs and systems. Hence, there is no effective ability to predict reactions and outcome based on 'pars pro totto' insight. In fact, unexpected responses to medications are often observed in elderly patients - stronger than expected in some patients, weaker than expected in others. The age related pharmacodynamics in elderly and old patients has clinical implications, here only to be mentioned the difficulty to adequately control blood pressure, and problems in administration of analgesic medications, opiates and anesthesia. The older the patient, the more challenging becomes the maintenance of homeostasis under stressful conditions. In other words, the balancing act that is life becomes more delicate. This largely impacts decisions on management, with particular emphasis on surgery.

Good-Old Rules of Clinical Examination

The 'good-old rules' regarding clinical examination of geriatric patients are substantiated by every-day practice and deserve to be reiterated [1-3]. As the patient becomes old, communication with the patient may become difficult and anamnestic details have to be collected from family members, friends and nursing staff. When you see an old patient with a plaster cast, a bandage or a splint or some other orthotic appliance, take it off and look at the skin. You have to see with your eyes what you are treating. You may be surprised more than once. If you are afraid to remove the splint or cast because of loss of reduction (or legal implications), take an X-ray examination and see if there is any reduction. If there is none you can proceed. If you still are afraid, ask the orthopedic surgeon to remove the cast and control the skin's condition itself. The skin is as important to the patient's health as any bone is, and an untreated pressure sore is life threatening. You can always use splints, boots or other orthotic appliance bought over the counter that can be taken off every day for inspection and treatment of the skin. Any immobilization conveys a risk that should not to be taken lightly. If there is no other alternative to treat the patient, make sure the immobilization appliance is well padded and that the skin cannot be macerated by accumulating moisture.

If you do not hear from the very old patient that he has pain, it does not mean he has none. A demented patient may be in pain without having a way to tell you about it. Sometimes it pays off to treat pain just to see if the patient becomes less confused. This will be the warning that he was in pain. Furthermore, cuts and bruises may bleed very little in this population. They may take months to heal. Do not be complacent with these lesions as they may complicate easily.

When examining a very old person, remember that he probably lost full range of movements many years ago, that trembling has become part of all-day life, and muscles have become good only for some routine activities and nothing more. Be gentle when moving body parts and proceed slowly! Do not take the risk of underestimating the patient’s general condition. The very old may be in stress but the vital parameters might appear to be normal. Fluid and electrolytes balance, anti-coagulation control, pressure sores control, avoidance of constipation are important and may become critical in the oldest. Caution is an imperative when administrating analgesics. NSAIDs may depress the respiration and may interfere with antihypertensive agents. Opioids must be used with care considering potential respiratory depression. Obviously, usual length-of-hospitalization standards are not applicable to very old patients. These patients usually need a longer stay in the hospital than younger elderly patients (a 70-year-old is young compared to a nonagenarian).

Last but not least, if there is need to treat the very old in the operating room, a one stage operation, of course, is the preferred option.

Case Histories

As this is a short review, I will describe cases that are more or less typical for the every-day practice.

Case 1 - wrist fracture An 87-year-old female sustained multiple contusions, abrasions and a right Colles fracture following a fall after being mugged and pushed when walking in the street.

Treatment considerations: This patient urgently needs to have her dominant hand functional again. A fracture reduction would be one more aggression to this old lady. In addition, most reductions at this age become ineffective well before consolidation, if not immediately. Therefore, nothing would be accomplished by reducing the wrist fracture. There are more threats relative to fracture reduction. Any reduction would require some kind of anesthesia that would confuse the patient more than she is already. Then, the plaster of Paris cast or other circular fixation would imperil her skin health. The old patient should not be treated with a cast. Someone has to inspect the skin daily and treat any cuts, bruises or sores, which cannot be seen through a plaster (Figures 1-3). Lastly, a good reduction is not a goal in this case, as it is in younger patients. The goal is a less traumatic treatment, daily inspection of the skin and early active mobilization conditioned by the patient's pain [4-6].

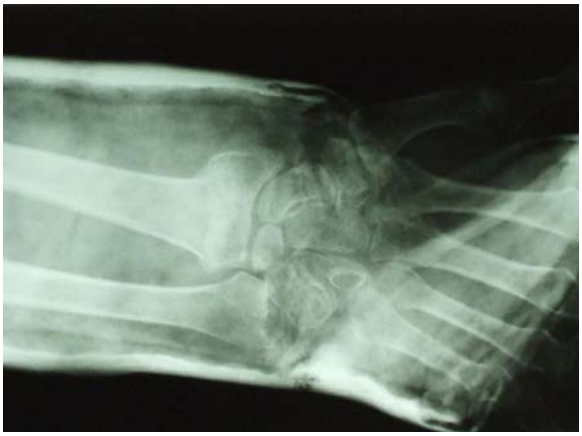

Figure 1: Radiography of old lady's wrist fracture a week after being treated by reduction and cast. There is no reduction so the cast can be of no help.

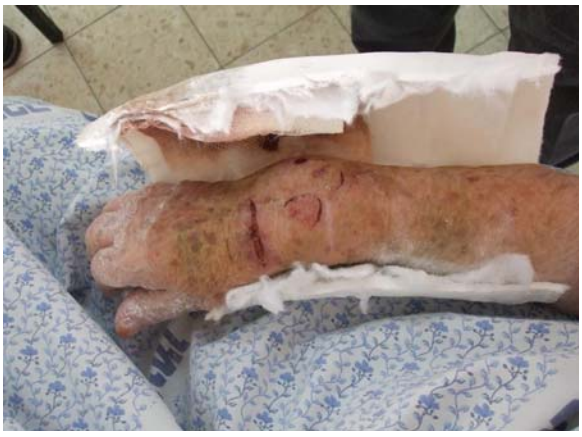

Figure 2. Open wounds covered by a circular cast, a few moments after opening the cast.

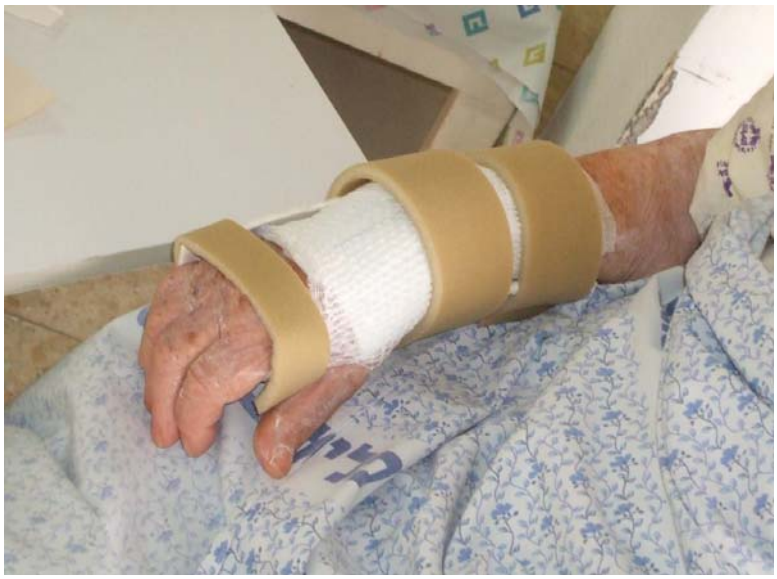

Figure 3. After fitting of thermoplastic custom made splint.

The best way to treat the fractured wrist is by a thermoplastic splint that the patient can adjust himself. The measure of a good outcome consists in the fast resuming of daily activities, with use of the fractured hand. If the patient has problems with walking that cannot be resolved by a cane, a walker with a platform attachment on the right side can be used.

The patient described above was treated with a thermoplastic splint. The fracture consolidated after a month. The cut in her forearm resolved without complications and the skin looked no different than in the other hand. After two weeks she was eating with both hands. She recovered full function after six weeks.

Case 2 - chest trauma An 84-year-old man fell from a ladder when changing a light bulb. He appeared to be somewhat confused and would speak only with his daughter. He complained of left lateral chest pain, which was aggravated by palpation and respiration. Movement was very painful. The pain was typical of chest contusion or rib fractures, but examination of chest X-rays was inconclusive. A way I use to inspect the rib radiographs is to look at the ribs when in a horizontal position (the ribs, not me). As I am used to read horizontal writing it becomes easier this way, and fractures suddenly 'appear', fractures my eyes did not detect in the usual way of looking at the chest radiograph. It appeared that this patient had three fractured ribs. No pneumothorax or hemothorax were apparent. The origin of the chest pain may be in the periosteal tissue and intercostal muscle tear and in the local hematoma produced. This patient tries to lessen the pain by limiting the chest movements. At younger ages, this kind of antalgic hypoventilation may go without deleterious consequences, but at this patient's age, restricted ventilation may cause hypoxemia, hypercapnia, atelectasis or pneumonia.

If I do not see rib fractures in the radiograph, I will still prescribe the same treatment for the following reason: as the bone resisted the impact and the energy of the hit (no fractures apparent on X-rays) and dissipated the energy to the soft tissues, most likely hematomas resulted (which I cannot see in the radiograph) that are causing the pain.

Treatment considerations: This patient needs blood gases monitoring. To relieve his pain he needs to sit or at least recline to permit his diaphragm to work more efficiently. He may be treated with analgesic medications that specifically do not inhibit respiratory drive. If the pain remains severe in spite of antalgic medications, consider doing an intercostal block with lidocaine. The problem with this block is the risk of a pneumothorax, so ask a specialist to do it [8]. Good people or an 'experienced nurse' with old ideas will try to limit movement of the chest with pillows or, worse, by using bandages. This has to be avoided as it may compound the problem with lung or skin complications. The impossibility to breath unimpeded is very dramatic and stressful, so the patient needs a lot of reassurance. If the trauma caused only hematoma, the problem will resolve within a week or two and if it was a fracture it may take 3 to 4 weeks.

Case 3 - elder abuse A 91 year-old widow lived alone at her home as she did for the last 50 years. She is now dependent in most activities of daily life. Three years ago, her daughter hired a young caregiver to live with and care for her mother. This situation was stable until 2 month ago, to everybody's satisfaction. The daughter told us that at that time her mother's interest in her surroundings and the ability to have a dialog with family members had diminished. She took her to the family physician, but nothing specific was found on physical examination and routine laboratory workup. I suggested to consider possible abuse by the caregiver leading to depression, or just intellectual decline. Now, there seems to be no orthopedic issue in this case, but the possibility of elder abuse has to be taken into account. Living with nonspouse family, friends, or other persons in a nonsupervised setting and a history of family disruption by widowhood may signal higher risk.

Elder abuse is a full chapter's worth [9]. As psychological abuse is most of the time involved, it will be difficult to obtain any information from the patient or the family. Awareness of possible neglect and abuse is many times a step forward to the diagnosis. Remember that most cases occur at home and not in institutions. Be careful to consult about the legal aspects of this diagnosis, as not only will the family be unhappy with your suspicion but also the patient. If there are physical signs, from the orthopedic point of view you'll see a battered or neglected patient with bruises and hematomas at different stages of evolution as well as fractures of face bones. All of these may be noticed in areas of the body that wouldn't usually get hurt during a fall, but that are typical of physical aggression. Delay in seeking medical help, dehydration, apathy, loss of weight, undermedication may also be part of this syndrome.

Case 4 - humerus fractures (shoulder and proximal humeral shaft) An 87 year old man fell on the stairs 'for the first time in his life', when going to a blind date. He lived independently in a protected residential area. A displaced fracture below the surgical neck of the right humerus was diagnosed and treated with a heavy plaster cast, which hindered him in activities of daily living. The reason for this cast was the theoretical axial traction produced by the weight of the cast that was supposed to keep the humerus more or less reduced. The patient was hospitalized in the rehabilitation department a week later. He complained of pain from the shoulder to the hand. He couldn't do any us of his hand. The first thing to check was the integrity of the neural and circulatory supply of the limb. Second the skin's condition. A very extensive hematoma in different stages of resolution could be seen. The hand was swollen and the patient could not bend his fingers properly (Figure 4). A radiography showed

no reduction at all and hardly any contact between the proximal and distal parts of the fracture. The cast was removed and a sling built from a stockinette fabric. A few hours later the swelling of the hand remitted and the pain was reduced to the area of the shoulder. Instructions were given to begin active range of movement exercises and he was sent to an occupational therapist.

Figure 4. Displaced fracture below the surgical neck of the right humerus. Deformity of the shoulder, extensive swelling and hematomas of the upper limb were seen after removing the plaster cast.

Treatment considerations: at advanced ages the best solution is to do what is less challenging to the patient's limb [1]. This is true for the shoulder and humerus shaft. Sometimes these fractures are treated by a percutaneous pin or intramedullary nailing, which should help to keep the axial reduction of the humerus. However, in the very old this procedure usually does not work. One time I was able to remove one of these nails without any instrumentation and without any effort after it found its way through the skin. A sling for 6 weeks and active mobilization as soon as possible are the best alternative. This treatment will reduce to a minimum the shoulder contracture that is associated with this kind of fractures. Recent dislocations are best reduced. A demented patient may have a dislocation diagnosed long after it occurred; in such a situation it is best to leave the shoulder as it is and try rehabilitation treatment.

Case 5 - muscle or tendon tears A 77-year-old man was sitting in his dining room when a lady visitor arrived. He rose politely, took a chair and moved it to allow the lady to sit down. The chair fell from his hand and, instantaneously, acute pain arose in his back. The next day

he felt better but he had difficulty in using his left arm. At examination a rare complete Latissimus Dorsi tear was diagnosed (Figure 5).

Case 6 - bilateral Achilles tendon tear For the last year, an 82 year-old man walked unsteadily. He consulted consecutively a neurologist, a chiropractor and a podiatrist. He was treated for neuropathy, 'disadjustments' and cavus, respectively. He would like to walk but was worried that he could fall. On physical examination bilateral Achilles tendon tear was suspected (Figure 6). The diagnosis was confirmed by ultrasound. There were two therapeutic options: orthotic splints (AFO: ankle foot orthotic splint) which can stabilize the ankles at 90 degrees, or a pair of good high leather shoes or boots which may do the same. The patient chose the boots and resumed his hobby.

Other common tears at old age can be seen in the quadriceps muscle and the biceps brachii, but every muscle or tendon can tear, especially when challenged by excentric loading, as it happened in the case of the latissimus dorsi muscle [10-12]. Patients treated with quinolone antibiotics at this age are 20 times more prone to sustain a tear, especially when combined with steroids [13,14].

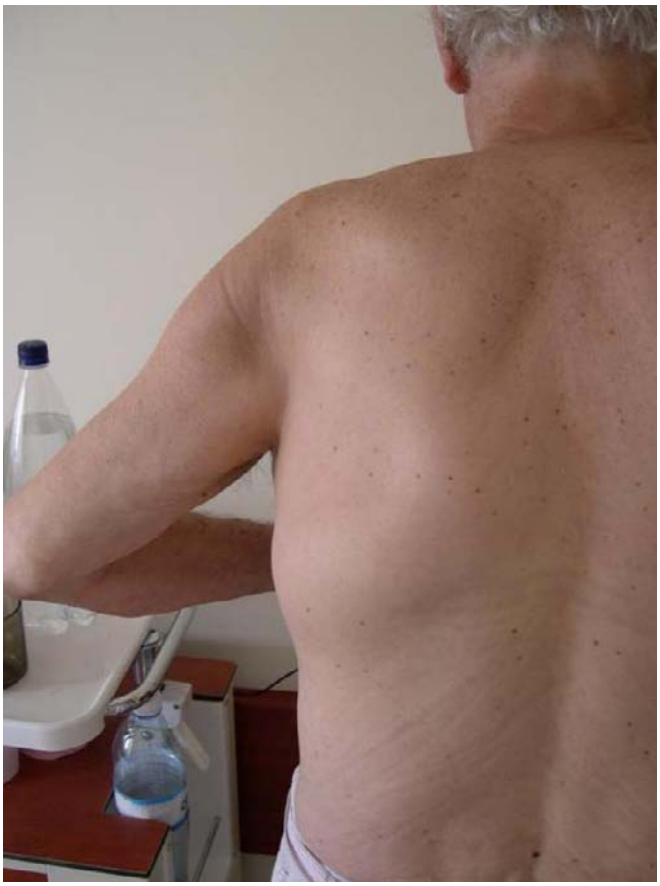

Figure 5. Complete latissimus dorsi tear.

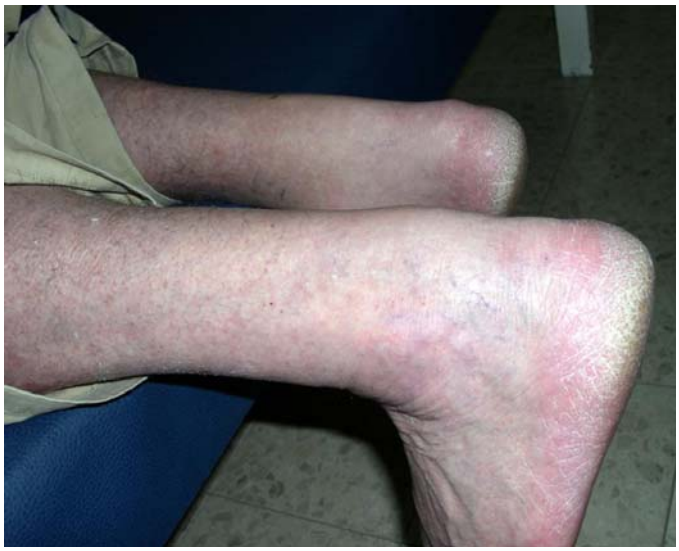

Figure 6. Old Achilles tendon tear.

Treatment considerations: It is surprising how little impairment most of these tears produce in the very old. There is no point in having surgery for most of them. But a complete tear of the quadriceps must be treated with surgery and a splint. The day after surgery the patient may begin walking exercises.

Case 7 - spine fracture An 88-year-old woman fell into her seat (this is an axial trauma). This was not her first serious fall, in spite of using a walker for ambulation. After several days she was still complaining of severe low back pain. She was able to move the lower limbs and also to walk. On X-rays, wedge fractures at thoracic and lumbar levels were apparent as well as ostheoarthritic deformations and osteoporosis. This old lady's history suggests that some of the vertebral fractures were old, but the current pain may be due to a new fracture somewhere in the spine. At her age surgery is a big risk, but new minimally invasive surgery and percutaneous techniques make possible a solution to deformity and pain with smaller risk compared with standard surgery [15,16]. Treatment will in most cases be symptomatic: rest and pain control and if the spine deformity is severe a brace. This type of wedge fractures carries a very small risk of spinal cord injury.

If a cervical fracture is suspected, immediate immobilization is a must. The first thing to be done is to check the stability of any fracture sustained, since a spinal cord injury could have catastrophic consequences, especially in the cervical spine. Diagnosis can be done only by a specialist, in a proper environment.

In Focus

Hip fractures Very old patients that suffer a hip fracture can be divided in three categories [17,18]. Those who suffered *a car accident* not only have a fracture but usually have several additional injuries and life could be in immediate danger. A second category are those *patients who fell while walking*; most are in urgent need of orthopedic surgery, the

sooner the better. At very old age, a Moore hemi-arthroplasty for capital fracture should be preferred. This operation will achieve results as good as total hip replacement, the latter procedure being much more traumatic and more complication prone. We should remember as a rule, that arthroplasty is associated with significantly greater mortality than osteosynthesis. Lower neck fractures should be treated with a nail, the nailing procedure being feasible with minimal invasive surgery. In case the surgical risk is high and the patient is not operated, the solution proposed is to begin mobilization after a few days and ambulation as soon as pain permits. The resulting shortening of the limb can be treated with a custom made shoe. The third category refers to *wheelchair bound patients*. In this situation there is no point in having the patient operated. They should go back home as soon as possible.

Pelvis fractures In the very old there are two main etiologies for traumatic pelvis fracture: a car accident or a fall. A car accident is a category in itself. A fall may happen when a person is transferring from a wheelchair to the toilet, while walking or when trying to seat in a low chair and falling into it. Most fractures in the very old are treated by rest and later on mobilization. If the fracture affects the acetabulum and the patient was until recently ambulating a zealous orthopedic surgeon could consider treating the patient by traction, with all the hazards that this kind of immobilization may entail for the very old. It is better to limit ambulation than to have traction or an operation. Still, in selected cases an operation is a necessity.

Car accidents In our days we see very old people driving cars and powered wheelchairs on the streets. Very old people involved in a car accident should be treated intensively, but only a few will survive for a long time. The first must, still at the site of the accident, is to perform a cardio-respiratory check up and appropriate treatment. From the orthopedic point of view, we need to make sure that there are no fractures or dislocations. Any splint used by the emergency team in the field should be removed to check the condition of the skin. A dislocation must be treated at the first opportunity that the patient is administered anesthetics. Never try to reduce a dislocation in the very old without anesthesia. Fractures will be treated by splints to reduce edema and pain. A very old patient need to have his occiput, back, buttocks and heels checked and protected for pressure sores till he becomes mobile. For this reason it is better to avoid definitive treatment of some fractures than to have a traction that hinders nursing care.

Concluding Remarks

The clinical presentation of trauma as well as treatment of trauma in the old and oldest persons is different compared to younger persons. The dissimilar clinical features, risks of surgery, and outcome are not only related to the patients' age but also to their general condition, chronic ailments, the drive and level of activity. More so than in the younger persons, the old person's social environment may contribute to the difference between a satisfactory result, with resumption of daily life at same level as before the trauma, or functional decline and dependence on others.

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