Sepsis and Organ Dysfunction

Epidemiology and Scoring Systems
Pathophysiology and Therapy

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Sepsis and Organ Dysfunction

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ORGAN FAILURE ACADEMY

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Sepsis and organ dysfunction are different entities. In ICU patients these conditions may appear concomitantly more often than would normally be the case for other pathophysiological and clinical manifestations. The development of organized intensive care units around the world over the past decades has increased the possibility for survival in patients ranging from the newborn to the oldest critically ill. Researchers and clinicians have developed a whole set of strategies for the prevention and management of sepsis and organ failure. Advances in biotechnology became indispensable to monitor organ function and provide long-term support in multiple organ dysfunction. The prevention of infections – whenever possible – is a golden standard. Its implementation, however, though easy in theory, may come up against some concrete difficulties in practice. So, Systemic Inflammatory Response Syndrome (SIRS) remains a mysterious condition, while for sepsis it is still very difficult to reach consensus on its definition, on the procedures used to perform a correct diagnosis, or the administration of a selective antibiotic, or the timing of re-laparotomy. Besides, the mortality rate for patients suffering from sepsis and organ dysfunction remains high. The epidemiological aspects and the complexities of sepsis and organ dysfunction are a well-known phenomenon. The use of prognostic indexes may be an important tool for patient selection. To date, however, it is not yet clear whether the use of scores is of actual benefit to individual patients or if it improves therapy. Mediators are regarded as vital elements for survival. However, these molecules are often messengers of ill fate in terms of patient outcome. The problem is to understand how they work, so the enigma remains unsolved. Procalcitonin is one of the latest mediators to have been proposed as an important marker of infection.

Prostaglandins are a more persistent finding in the bloodstream, so modulating prostaglandin metabolism in sepsis has provided few answers so far and many questions remain open. The issue of oxygen delivery optimization in sepsis is of paramount importance. General consensus has now been achieved concerning the role of inotropic and vasoactive drugs to maintain pressure in the cardiovascular system. The maintenance of organ perfusion is a different matter, so oxygen delivery and consumption ratios in sepsis remain controversial. In recent years monoclonal antibodies and receptor blocking agents have represented important potential advances in the management of sepsis, though unfortu-

nately in many international trials the large amounts of negative data outweigh the encouraging results obtained in some sub-groups of patients.

So, the high cost of research and the difficulties encountered in enrolling patients have led to what some termed the Bermuda Triangle for pharmaceutical industries. Measuring ipH is a valid tool to monitor gastrointestinal perfusion, and experimental and clinical data on hepatosplanchnic circulation is very encouraging. Systemic Digestive Decontamination (SDD) has proven to be effective in the prevention of Gram-negative infections. On the other hand, however, the role of bacterial translocation needs to be confirmed in the clinical setting. Consumption coagulopathy is a complication leading per se to multiple organ failure; heparin, aprotinin and antifibrinolytic agents often represent the treatment of choice, even though the mortality rate remains high.

In conclusion, it can be stated that there is no magic recipe for the prevention and treatment of sepsis and organ dysfunction. So it can be said that the future is likely to be characterized by both favourable and unfavourable developments. Actually, multiple therapeutic agents offer a series of options, but the answers for the future will come from a better understanding of the mechanisms regulating cellular functions, from the discovery of new mediators able to prevent apoptosis, as well as the ability to correctly explore immunologic dissonance.

Monitoring organ functional reserve and understanding messages in their mutual relationships are the next steps ahead. Some of the tasks outlined above represent a real challenge for researchers and clinicians at the dawn of the XXIst Century.

Arthur E. Baue
Giorgio Berlot
Antonino Gullo

Trieste. 19th November 1997

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Abbreviations

AIS, abbreviated injury score

AOSFSS, acute organ system failure scoring system

APACHE, acute physiology and chronic health evaluation system

ARDS, acute respiratory distress syndrome

ARF, acute renal failure

ASCOT, a severity characterization of trauma

ATI, abdominal trauma index

ATIII, antithrombin III

BI, burn index

BSS, Baltimore sepsis scale

CARE, clinical assessment, research and education system

CARS, compensatory anti-inflammatory response syndrome

CCSS, critical care scoring system

CHAOS, cardiovascular compromise, homeostasis, apoptosis, organ dysfunction, suppression of immune system

CIRS, cumulative index rating scale

CIS, cell injury score of Hirasawa

CRAMS, circulation, respiration, abdomen, motor, speech

CVP, central venous pressure

DEC, diethylcarbamazine

DIC, disseminated intravascular coagulation

DPE, daily prognostic estimates

ENAS, European North American study

EPI, endocrine prognostic index

FCI, functional capacity index

GCS, Glasgow coma score

G-CSF, granulocyte colony stimulating factor

GM-CSF, granulocyte macrophage-colony stimulating factor

HPI, hospital prognostic index

HR, heart rate

HTI, hospital trauma index

ICAM1, intracellular adhesion molecule 1

ICU, intensive care unit

IL-1, interleukin-1

IL-1ra, interleukin-1 receptor antagonist

IL-6, interleukin-6

IL-8, interleukin-8

IIS, injury impairment score

ISS, injury severity score

LOD, logistic organ dysfunction

LODS, logistic organ dysfunction system

LSI, limb salvage index

MAP, mean arterial pressure

MARS, mixed antagonistic response syndrome

MESS, mangled extremity severity score

MIP, macrophages inflammatory protein

MISGS, medical illness severity grouping system

MOD, multiple organ dysfunction

MODS, multi-organ dysfunction system

MOF, multiple organ failure

MPS, Mannheim peritonitis score

MSOF, multiple system organ failure

MTO, major trauma outcome study

ODIN, organ dysfunction and/or infection

OIS, organ injury scales

OSF, organ systems failure

PAF, platelet activating factor

PAP, plasmin-antiplasmin

PC, protein C

PNI, prognostic nutritional index

PODS, probability of death score

PRISM, pediatric risk of mortality

PSI, predictive salvage index

PT, prothrombin time

PTS, polytrauma score

ROC, receiver operating characteristic

SAPS, simplified acute physiology score

SCOUT, surgical complication outcome

ShO_2, hepatic venous oxygen saturation

SIRS, systemic inflammatory response syndrome

SMART, systemic mediator-associated response test

SOFA, sepsis organ failure assessment

STAR, staged abdominal repair abdominostomy

TAT, thrombin-antithrombin

TFPI, tissue factor pathway inhibitor

TISS, therapeutic intervention scoring system

TNF-α, tumor necrosis factor alpha

t-PA, tissue-type plasminogen activator

TRISS, trauma and injury severity score

TS, trauma score

u-PA, urokinase plasminogen activator

$\dot{V}O_2$, oxygen consumption

VS, ventilator score

WBC, white blood cell

EPIDEMIOLOGY AND CLINICAL COURSE OF SEPSIS AND MODS

Epidemiology and Clinical Course of Sepsis

L. ILKKA, J. TAKALA

Sepsis can be broadly defined as the systemic inflammatory response to infection. Sepsis is an important cause of morbidity and mortality in hospitalized patients. In intensive care patients, sepsis is one of the most common causes of prolonged intensive care and death. Accordingly, a sizable proportion of intensive care resources is used to treat patients with sepsis and sepsis-related dysfunction of vital organs. Despite this, the epidemiology and clinical course of sepsis has not been well defined. Lack of uniform definitions and criteria for sepsis has certainly contributed to this lack of information.

In the past, the term "sepsis" has been used quite loosely. It has covered bacteremia, clinical conditions consistent with infection, and verified local or systemic infections with variable sets of biochemical and clinical signs and symptoms (Table 1) [1-13]. It is self-evident that the selection of the criteria will have a major impact on any epidemiological and clinical data. The various definitions of sepsis have gradually converged to focus on the clinically obvious link between serious infection, and its systemic manifestations, especially organ dysfunction.

Verification of infection is usually regarded as a fundamental criterion. Because of the problems associated with positive cultures, especially bacteremia, new radiological findings consistent with infections as well as demonstration of gross infection foci have also been used. It is unlikely that one single definition would be practical for all purposes. For daily clinical routine, a low threshold of suspicion and aggressive search for infection foci is vital. On the other hand, therapeutic trials often benefit from much more rigorous criteria.

Every clinician is familiar with "suspected sepsis", where cultures are negative but the clinical signs and symptoms are consistent with the response to infection. These patients are treated without great problems of definitions. In contrast, for research purposes this term is problematic. It is too wide, and can include very heterogeneous patient population, and is heavily influenced by differences between clinicians. A systemic response closely resembling or even identical to sepsis may also be induced by non-infectious factors, including ischemia, major burns, or pancreatitis. For the purpose of this review, we use the term sepsis to indicate the systemic response to infection.

Table 1. Examples of various definitions or criteria for diagnosis of sepsis

Bacteremia [1, 2]
Documented by positive blood or body fluid cultures, or unmistakable evidence of a septic process [3]
Host response to a microbiological event (induced by the presence of bacteria, viruses, fungi...) [4]
A serious infection and the systemic response to infection [5]
The systemic response to infection. This systemic response is manifested by two or more of the following conditions as a result of infection: 1) temperature > 38 °C or < 36 °C, 2) heart rate > 90 beats/min, 3) respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr / < 4.3 kPa, and 4) white blood cell count > 12 000 cells/mm^3, < 4000 cells/mm^3, or > 10% immature (band) forms [6]
Septicemia = systemic disease associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood [7]
Clinical evidence suggestive of infection plus signs of a systemic response to the infection (all of the following): tachypnea (> 20 breaths/min, or if mechanically ventilated, > 10 L/min), tachycardia (> 90 beats/min), hyperthermia or hypothermia (core or rectal temperature > 38.4 °C or < 35.6 °C) [8]
The presence of various pus-forming or other pathogenic organisms and/or their 'toxins' in the blood or tissues [9]
A systemic response to infection and inflammation that is usually characterized by a toxic clinical picture, including fever or hypothermia, tachycardia, tachypnea, and mental obtundation [10]
A clinical response characterized by alterations in one or more of temperature, white blood cell count, and mentation in association with a hyperdynamic hypermetabolic state [11]
Fever or hypothermia (temperature > 38.3 °C or < 35.6 °C); tachycardia (> 90 beats/min in the absence of beta-blockade) and tachypnea (respiratory rate > 20 breaths/min or the requirement of mechanical ventilation); and either hypotension (systolic blood pressure ≤ 90 mmHg or a sustained drop in systolic pressure ≥ 40 mmHg in the presence of an adequate fluid challenge and the absence of antihypertensive agents) or two of the following six signs of systemic toxicity or peripheral hypoperfusion: unexplained metabolic acidosis (pH ≤ 7.3, base deficit of > 5 mmol/L, or an elevated plasma lactate level); arterial hypoxemia (PaO_2 ≤ 75 mmHg or PaO_2 / FIO_2 < 250); acute renal failure (urinary output of less than 0.5 ml/kg/hour; elevated prothrombin or partial-thromboplastin time or reduction of the platelet count to less than half the baseline value or less than 100 000 platelets/mm^3; sudden decrease in mental acuity; and cardiac index of more than 4 L/min/m^2 of body surface area with systemic vascular resistance of less than 800 dyn · sec · cm^{-5} [12]
Known or suspected (gram-negative in this study) infection plus at least one of these signs of sepsis: 1) fever or hypothermia: > 38.2 °C or < 36.5 °C, 2) tachycardia: > 90 beats/min, 3) tachypnea: > 20 breaths/min plus at least one of these signs of organ dysfunctions: 1) hypoxemia: PaO_2 / FIO_2 ≤ 280, 2) increased serum lactate concentration: above normal value for laboratory, 3) oliguria: < 0.5 mL/kg of body weight/hr, 4) altered mentation: Glasgow Coma Scale < 15, or decrease ≥ 1, 5) new coagulopathy: unexplained [13]

For standardizing the terminology, a North American consensus conference published in 1992 the recommendations for the definitions of sepsis and its sequelae [6]. Sepsis was defined as systemic inflammatory response in the presence of infection, with two to four clinical manifestations (Table 2) [6]. The term "systemic inflammatory response syndrome" (SIRS) was proposed to be

Table 2. The definitions of ACCP/SCCM consensus conference

Infection	Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms
Bacteremia	The presence of viable bacteria in the blood
SIRS	The systemic inflammatory response to a variety of several clinical insults The response is manifested by two or more of the following conditions: temperature > 38 °C or < 36 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr (< 4.3 kPa), and WBC > 12 000 cells/mm^3 or < 4000 cells/mm^3 or > 10% immature (band) forms
Sepsis	The systemic response to infection. This systemic response is manifested by two or more of the following conditions as a result of infection: temperature > 38 °C or < 36 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr (< 4.3 kPa), and WBC > 12 000 cells/mm^3 or < 4000 cells/mm^3 or > 10% immature (band) forms
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and hypotension abnormalities may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation, along with presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured
Hypotension	A systolic blood pressure < 90 mmHg or a reduction > 40 mmHg from baseline in the absence of other causes of hypotension
Multiple organ dysfunction syndrome	Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

used in cases of an evident systemic response in the absence of a verified infection. As in the definition of sepsis, the criteria of SIRS include alterations in two to four parameters: temperature, heart rate, respiratory rate and leucocyte level.

In later epidemiological studies using these consensus conference definitions it has been clearly shown that SIRS is a too sensitive and nonspecific tool for research and practice purposes [4, 14, 15]. The vast majority of ICU patients and even hospitalized patients fullfil the criteria of SIRS in some phases of the hospitalization. The fullfilment of these criteria alone appears to be without clinical relevance and have no value for guiding the decisions of treatment or predicting outcome of patients.

Still, some SIRS patients are progressing further to sepsis or even septic shock states. The problem is how to select the right patients from large population. It is apparent that these rather arbitrary criteria need to be considered with other criteria, for example for including patients to prospective clinical or epidemiologic studies.

Epidemiology

The epidemiology and especially the clinical course of sepsis are not well known. The number of prospective epidemiologic studies with sufficient patient samples is sparse. Two larger European prospective epidemiologic studies of SIRS and sepsis-related states using ACCP/SCCM-definitions were published in 1995. Rangel-Frausto et al. studied 3700 patients admitted to three critical care units and three wards [14]. SIRS seemed common about 20% patients progressed to septic shock. The rates of positive blood cultures, end-organ dysfunctions, and mortality were related to the severity of the systemic inflammatory response. In the Italian sepsis study with 1100 patients SIRS was again a usual phenomenon at the time of admission [15]. As well as in the former publication, in this study also the mortality seemed to be related to the severity of sepsis, but no prognostic differences were observed between SIRS patients and patients without SIRS.

Two larger prospective studies evaluated the prevalence and incidence of ICU-acquired infections and sepsis-related states. A 1-day cross-sectional prevalence study of about 10,000 patients showed nearly half of the patients being infected during their ICU stay [16]. Another multicenter study focusing on severe sepsis showed that this state occurred in nearly 10% of ICU admissions, and that only three of four patients presenting clinical sepsis had documented infection [17].

It is well known and established that ICU patients are at increased risk for nosocomial infections. Less than 10% of hospitalized patients are treated in ICUs, but patients needing intensive care have about one fourth of all nosocomial infections [18]. Hospitalized patients have prevalence of nosocomial infection between 5 and 17% [16]. The prevalence of infections among intensive care patients has been reported to vary from 15 to 40% [19]. The risk of acquiring infection increases with the stay in the ICU and with the use of invasive devices.

The type of pathogens responsible for infections in ICU have changed during last decades [18]. In the 1960s and 1970s Gram-negative pathogens were predominantly causative. Later Gram-positive bacteria have become increasingly responsible. Especially the proportion of coagulase-negative staphylococci, methicillin-resistant Staphylococcus aureus, and enterococci has been increasing worldwide. Gram-positive and Gram-negative bacteria cover infections in roughly equal proportions. The rate of anaerobic bacteremias have decreased, with Bacteroides fragilis being the most common [20]. The amount of fungal infections have been greatly rising, especially caused by Candida species [21]. Candidemias account for under 10% of positive blood cultures, but the mortality rate in these cases is over 50%.

Also the profile of infection foci has changed during past decades [18]. It differs between ICUs and general wards. In the former respiratory tract infections are the most usual, whereas in the latter urinary tract infections predominate. The rate of blood stream infections have increased 5 to 10 fold compared

to earlier decades, covering now more than 10% of infections in hospitals, and 15% of ICU infections. More than 40% of these infections are associated with catheters. Pneumonia and other respiratory tract infections are the leading foci in infected ICU patients, covering about half of infections. Urinary tract is the source in about 10-20%. Other foci, such as wound, upper airway, gastrointestinal or central nervous system infections account for about one fourth of infections [16-18].

Mortality is related to the severity of sepsis, the type of infection and bacterial etiology. The crude mortality of infected patients varies greatly, from 10 to 80%, depending on the type of the ICU and definitions of sepsis used [19]. Rangel-Frausto et al. showed the mortality rates to increase in the hierarchy from SIRS and sepsis to severe sepsis to septic shock [14]. SIRS-patients had one month mortality of less than 10%. Half of the patients progressing to septic shock died. This is consistent with reports in the literature.

Pneumonia and bacteremia as a cause of sepsis are increasing mortality about two to three fold [16, 22]. Late-onset pneumonias with high-risk pathogens, such as Acinetobacter or Pseudomonas species, increase the risk to several fold [22]. Multiresistant organisms, for example vancomycin-resistant enterococci or methicillin-resistant Staphylococcus aureus contribute also to greatly increased risk of death. Gram-negative organisms as a whole group and coagulase-negative staphylococci seem to carry a lesser risk than other organisms. Multiple sources of sepsis is a phenomenon clearly associated with poor prognosis [17].

Clinical course of sepsis

The clinical progress of sepsis is poorly known. The duration of ICU stay and hospitalization, and incidence of organ failures progressing after sepsis are better established. Infections prolong the hospitalization time by several days. Several matched case-control studies assessing the extra length of hospitalization due to infection have been published [22]. Dependent on the type of infection, the excess length of stay has varied among ICU patients between one and two weeks. In a study of bacteremic ICU patients the median length of hospitalization was 40 days compared to 26 days with matched control patients without infections [22]. In sepsis of other foci the excess lenght of stay has been reported to be around one week.

In the study of Rangel-Frausto et al. 56% of sepsis patients were septic immediately on the day of admission. Similarly 42% of patients in severe sepsis and 29% of septic shock patients were in their categories already during the day of admission. The median intervals from one category to another were variable. The interval times with culture-negative patients were similar to that of patients with confirmed infection. The 28-day mortality in this study was 9%, but an

additional proportion of patients died within six months of discharge from ICU. In the study of 1052 patients in severe sepsis, the median length of ICU stay was over one week [17]. It greatly differed from survivors to nonsurvivors, 34 days and 4 days, respectively. One third of patients stayed in the ICU more than two weeks.

End-organ dysfunctions are common in sepsis. In the past, multiple organ failure (MOF) was thought to be caused by uncontrolled or undiagnosed infection [11]. Later it has become clear that organ dysfunctions can develop and progress in the absence of uncontrolled infection, and the treatment of the infection may fail to prevent the development of MOF. In the study of Rangel-Frausto et al. end-organ failure rates increased with the number of SIRS criteria [14]. The attack rates of acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), acute renal failure (ARF), and shock were quite similar in SIRS and sepsis patients (about 4, 16, 13 and 21%, respectively). Patients progressing to severe sepsis and septic shock had increasing rates of these dysfunctions in each stage (respectively 6, 18, 20, and 25% in severe sepsis, and 18, 38, 45, and naturally 100% in septic shock) (Table 3).

Table 3. Attack rates for end-organ dysfunction

Syndrome	No. of patients	ARDS (%)	DIC (%)	ARF (%)	Shock (%)
SIRS with 2 criteria		2	8	9	11
SIRS with 3 criteria		3	15	13	21
SIRS with 4 criteria	Total in SIRS 2527	6	19	19	27
Positive culture sepsis	649	6 *	16 *	19 *	20 *
Negative culture sepsis	892	3	20	5	27
Severe sepsis with positive cultures	467	8	18	23 *	28 *
Severe sepsis with negative cultures	527	4	17	16	22
Septic shock with positive cultures	110	18	38	51	100
Septic shock with negative cultures	84	18	38	38	100

* = p value < 0.05 between culture positive and culture negative stages.

(Modified from [14])

In summary, sepsis is an important reason for morbidity and mortality in ICU patients. Despite the vast amount of resources used for its treatment and in the search of new therapies, the epidemiology and clinical course of sepsis remain poorly documented. In order to better understand the pathophysiology and the develop of new therapies, a more defined description of this syndrome and its clinical course is needed.

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The Complexities of Sepsis and Organ Dysfunction

A.E. BAUE

Inflammation in itself is not to be considered as a disease ... and in disease, where it can alter the diseased mode of action, it likewise leads to a cure; but where it cannot accomplish that solitary purpose... it does mischief.
John Hunter: A Treatise on the Blood, Inflammation, and Gunshot Wounds
London, 1794 [1]

I am pleased to join Professor Gullo in welcoming all of you to the Sixth Organ Failure Academy Meeting here in Trieste, Italy, and to the program today, "An update on the pathophysiology of and potential therapy for sepsis and organ dysfunction".

Much has happened since the Organ Failure Academy was established by Professor Gullo. We have learned many things and gradually patient care has improved. The expectation that there would be magic bullets to solve many of our problems has not been fulfilled [2]; thus, we must meet today comparing notes on what we know and what we must learn. The power of molecular biology to provide information and solve problems has yet to meet its full potential. We look forward to hearing from all of you and to have important questions raised by those of you in the audience.

There are many complexities concerning sepsis and organ dysfunction and there is also considerable confusion about them. There are six complexities which I will comment upon in this brief introduction. Some of my questions and the complexities related to them will be reviewed by many authors in the present book. These six are shown in Table 1. I will review each of these in some detail.

Review of complexities

Sepsis

Although we have a general idea as to what it is included with sepsis, the word means many different things to different individuals. Is it due to infection or is it

Table 1. Complexities (and confusion) about...

Sepsis - What is it? And how do you treat it?
Terminology - Acronymania - Does this help us?
Inflammation - Is it an organized sequential system which can be blocked, stimulated or modulated?
Pro- and Anti-inflammatory mediators - Can we time their activities so as to intervene?
There are many biologic conundrums (puzzles) or paradoxes
The causes of organ dysfunction and failure are complex

not? What is the organism? How do we define bacteremia and how is it different from septicemia? What is the sepsis syndrome? Roger Bone went to great lengths to try to get us to agree on terminology about the sepsis syndrome, believing that it was either due to infection or to an inflammatory reaction; however, there was never general agreement about this [3]. Severe sepsis is another matter and then, of course, there is septic shock. If there is an inflammatory process, what is it from? What causes it and how does it produce its problems? Tissue injury, whether due to trauma or to a planned operation or therapeutic event, requires inflammation in order to heal. Can there be too much inflammation? Can overwhelming inflammation be harmful and produce, not only toxicity, but actual death? In other words, do we self destruct if the inflammatory process and the injury is overwhelming [4]?

Finally, how do we treat all of these? Can we get away from specific diseases and specific infections with specific cultures of abscesses and of the blood to the concept of treating general phenomena such as SIRS and MODS? This is a big and difficult question.

Complexity of terminology

There seems to be continuous development of new terminology and we must question whether this has helped us. I mentioned earlier the attempt of Roger Bone to get everyone to agree on the sepsis syndrome but this did not happen. Then the concept of SIRS and MODS was developed even though MOF seemed perfectly acceptable earlier [5]. The definitions of SIRS and MODS and MOF are known to all of you and to the reader; however, these terms or expressions are not treatable. The patients having these expressions of different diseases can be treated for the disease but not the manifestations alone. These are constructs, or definitions of being sick; thus, there is no therapy for SIRS or MODS or MOF other than to try to prevent SIRS from becoming MODS and that from becoming MOF. How would you treat SIRS? Therapy of each aspect of SIRS is shown in Table 2. Obviously this is ridiculous. Vincent raised serious questions about the concept of SIRS in an editorial entitled "Dear SIRS, I'm sorry to say that I don't like you" [6]. In this article, he states his belief that SIRS is too sen-

sitive and does not help us understand the pathophysiology and does not help in clinical trials or in practice. He concludes by stating: "Dear SIRS, I'm afraid we don't need you". Now Bone has made a new proposal and that is the use of CARS, MARS and CHAOS [7]. This suggests to me a form of acronymania. Bone's proposal for CARS, MARS and CHAOS is shown in Table 3. Perhaps Bone stands for biologically occult but natural explanations*.

Table 2. Early treatment of SIRS

Temperature
a) If low, warm patient with warming blankets, extracorporeal warming circuit, warm i.v. fluids, irrigate peritoneal cavity with warm saline
b) If high, use external cooling, cool bath, rectal aspirin, etc
Rapid heart rate
Slow with calcium channel blockade, rapid acting digitalis, etc
Rapid breathing
i.v. morphine, other sedation, intubation, paralysis, and controlled ventilation
White blood count
a) For a low WBC - give G-CSF
b) For a high WBC - consider chemotherapeutic agents to control bone marrow

Table 3. MOF, MODS, SIRS and now...

CARS	Compensatory, antiinflammatory response syndrome
MARS	Mixed antiinflammatory response syndrome
CHAOS	Cardiovascular compromise (shock)
	Homeostasis
	Apoptosis
	Organ dysfunction
	Suppression of the immune response
BONE	Biologically occult but natural explanations
Of what therapeutic benefit are these terms?	
What will Bone/they think of next?	

My question is: Of what therapeutic benefit are these terms? What will they think of next? How much longer must we invent new terminology which does not help with therapy and perhaps does not even help with our understanding of these disease processes?

Finally, I would define acronymania as shown in Table 4. The likelihood of being able to lump together a lot of diverse infectious and injurious processes

* We are all sorry to learn of the untimely death of Roger Bone in the spring of 1997 after a long illness. We will miss his leadership.

under some generalized description is not going to allow us to treat patients more effectively. I have made a plea for breaking down all of these things into specific disease processes so that we can treat a disease rather than a construct or an acronym.

Table 4. Acronymania

Basic antiinflammatory response (BARS)
Compensating antiinflammatory response (CARS)
Functional antiinflammatory response (FARS)
Mixed antiinflammatory response (MARS)
Whole antiinflammatory response (WARS)
All of these may lead to CHAOS

Inflammation

"Natural forces are the healers of disease". Hippocrates, 460 B.C. Epidemics VI, VI

All of the problems of injury, operation, infection, sepsis, or inflammatory diseases require an inflammatory process to overcome the illness, if possible. John Hunter described the reactions to injury as "inducing both the disposition and the means of cure" [1]. As mentioned earlier, if the inflammatory process becomes excessive, it is believed now that this can be self destructive as well. However, the problem is that sepsis and inflammation may not be an organized sequential system. Those that have studied it extensively or actually observed it believe that there are many vagaries and it is not a process that can be understood well because of its variation on the theme. As Lewis Thomas stated [8],

"First, I would like to construct the straw man that I shall need to demolish before getting on. Nobody really believes it, but let us pretend that it is the general belief that inflammation really exists as an entity among biologic mechanisms, that represents an orderly sequence of time and coordinated events, staged to occur in such a way that the host is protected against a foreign adversary and able to minimize damage to his own tissues, kill off the adversary and finally tidy up the place and make whatever repairs are necessary. This is my straw man. I begin by saying that there really is no such mechanism.

I suspect that the host is caught up in mistaken, inappropriate and unquestionably self-destructive mechanisms by the very multiplicity of defenses available to him which do not seem to have been designed to operate in net coordination with each other. The end result is not defense; it is an agitated, committee-directed harum-scarum effort to make war, with results that are markedly like those sometimes observed in human affairs when war-making institutions pretend to be engaged in defense".

The question then is - If inflammation is necessary for survival, can it be controlled if it is excessive? Can it be blocked, stimulated or modulated and are

multiple agents required to do that? So far, single agents have been quite unsuccessful.

Mediators

We now know about any number of proinflammatory mediators. We more recently have learned about antiinflammatory mediators. There are a multitude of mediators in both systems. There is natural control of the inflammatory process. There are multiple enzyme cascades which serve biologic functions. As we learn more about them and, as more mediators are discovered, we learn that it is a very complex system that defies sequential change and modulation. I have called this a modern "Horror Autotoxicus" [4], a term borrowed from Ehrlich and Morgenroth who predicted in 1905 that autoimmune reactions would be a "Horror Autotoxicus" [9]. Can we control nature? Can we control a necessary process that becomes excessive? When does it become excessive and how? How do we get it back to baseline without getting the patient or the animal into more difficulty?

Biologic conundrums - Puzzles or paradoxes?

There are a number of circumstances that we now know about where there are puzzles or paradoxes or conundrums in the information about various mediators. Too much of a certain mediator is bad but too little is a disaster. One can prepare a long list of such factors where a substance, on one hand, is helpful but, if given in another circumstance or in another organ system, creates a disaster [10]. Can we hope to understand these conundrums and deal with them? Certainly we can strive toward that. However, again, the complexity of these reactions is most impressive. Can we then work in between, for example, can we control tumor necrosis factor? If an animal is given an injection of endotoxin or gram-negative bacteria, or if a small dose of endotoxin is given to a normal human volunteer, there are deleterious consequences which are mediated in good part by endotoxin which activates tumor necrosis factor (TNF) [11, 12]. In that circumstance, if one is to receive a bolus of endotoxin or bacteria, a monoclonal antibody to TNF would be protective so long as it was given before the insult [13]. How does one know that one is about to receive a bolus infusion or injection of endotoxin? In contrast, if a monoclonal antibody is given to an animal and then the animal is given a clinically relevant form of peritonitis, the mortality is much higher in those animals that received the monoclonal antibody to TNF [14]. How can we have it both ways? If, in one circumstance, TNF is necessary but, in another, it is a disaster, how can we decide beforehand what the circumstance of that patient is? There are many such biologic conundrums, which must be better understood, some of which are shown in Table 5.

Causes of organ dysfunction/failure

There are many causes or reasons why remote organs away from the site of the injury or away from the site of the insult or infection may become dysfunctional or fail (Table 6). Obviously, with trauma, there may be pulmonary contusions resulting in pulmonary failure or dysfunction, and the same with the myocardium, the gastrointestinal tract, bones, muscles, metabolism and other factors. However, a number of problems produce remote organ dysfunction or failure when they occur. First among these is ischemia and dysoxia. Where there has been a prolonged period of ischemia, such as with a low cardiac output, organ damage occurs. Ischemia/reperfusion will also do this when there has been a period of ischemia such as ischemia of the lower extremities during repair of an abdominal aortic aneurysm. With reperfusion, metabolites and other substances or mediators from the area of ischemia return to the central circulation and damage the lungs and perhaps other organs. There is white cell activation with injury where oxidants are produced which may damage adjacent cells, particularly endothelial cells, and proteases such as elastase are activated which may damage tissues. There may be failure of antioxidants where they are used up or are not available. This also can be a cause of remote organ dysfunction.

In our early description of multiple organ failure after injury we described a one hit phenomenon or insult where a patient with a severe injury developed multiple organ failure initially in the first few days, or a second hit when a patient was resuscitated and seemed to be getting along and then later got into difficulty [15]. The first hit was injury and the second often seemed to be related to infection. This two-hit phenomenon has been confirmed by Moore et al. [16]. Then we learned about overwhelming inflammation as a cause of organ failure in what I have called a modern horror autotoxicus [4] after the original description from Ehrlich and Morgenroth [9].

Lipopolysaccharide or endotoxin from gram-negative organisms can also wreak havoc with an individual as can gram-positive exotoxins and other infectious organisms. Bacterial translocation may be a cause of difficulty, although this has not been documented in all types of human illness. Cytokine activation can be a problem. Inadequate resuscitation certainly occurs frequently. Finally, the hyperdynamic, hypermetabolic high oxygen consumption requirements of sepsis may be a problem [17]. Can we treat that by appropriate action to increase it? We will learn more about that this morning.

Table 5. Biologic conundrums

Anti-Il-6 mab given to endotoxemic mice yields increased IL-6	
Il-6 deficient mice with liver failure have defective hepatocyte reg	
Interferon gamma given to animals after injury decreased lethal abdominal sepsis	
Interferon gamma given to animals without injury increased lethality of bacteria	
TNF enhances antibiotic efficacy after hemorrhage shock	
LPS pretreatment protects lungs from hepatic ischemia/reperfusion	
Germ-free animals after hemorrhagic shock have increased survival but increased inflammatory mediators	
Interferon gamma	primes only a subpopulation of PMNS (leukocytes)
Abscess model	Anorexia, weight loss and hepatic-acute phase response is due in part to IL binding to type I receptor. TNF binding is not required
Recombinant tissue pathway inhibitor	decreases abscesses in rats with peritonitis but increases bacteremia and death
A leukocyte CD18 mab	increases endotoxemia and CV injury with septic shock
Intestinal permeability is increased by trauma and shock	but there is no relation to septic complications
Polymyxin decreased plasma endotoxin	but there was no decrease in sepsis scores, IL-6 levels or mortality
High TNF levels	associated with survival in patients with abdominal septic shock
Immune-enhancing patients	exaggerated immune response and increased ARDS
TNF mab	protects against endotoxin infusion but increases mortality with CLP
Macrophage-depleted mice	increased systemic bacterial translocation decreased systemic toxic response decreased mortality
TNF deficient c3H/HcJ mice but	had increased survival from hemorrhagic shock
anti-TNF mab →	abolished increased TNF but did not increase survival
PGE_2	helps the liver contributes to immunosuppression
Inhibition of CD 11/18 (mab) - integrin receptor on neutrophils	with intrabronchial E. coli improved lung function but increased mortality
Prophylactic G-CSF upregulates immune response increased neutrophil function	may improve or worsen organ failure
Macrophage deficient mice (absent CSF-1)	→ decreased TNF, IL-1, GCSF and endotoxin induced bacterial translocation but morbidity and mortality same as in normal animals
LPS	Induces PGE_2 which decreases macrophage TNF production
NSAIDS	have beneficial effects on endotoxemia but increase TNF production
TGF-B	initiates and terminates tissue repair but sustained production increases fibrogenesis - tissue fibrosis
PGE2 but	produces immunosuppression
rats - 30% body burn but	Ibuprofen decreases certain aspects of immune function
rats - CLP	Ibuprofen decreases survival

Table 6. Cause of organ dysfunction/failure

Ischemia - Dysoxia (Hypoxia)
Ischemia/Reperfusion
WBC activation - oxidants/failure of antioxidants, elastase
One hit - two hits - Injury, Infection
Overwhelming Inflammation
The Horror Antitoxicus
LPS
Bacterial translocation
Cytokine activation
Inadequate resuscitation
The hyperdynamic, hypermetabolic high O_2 consumption of sepsis

Conclusion

We have made great advances in our understanding of the problems of inflammation, injury and infection. However, in spite of this knowledge, our abilities to treat patients successfully with these problems have been limited. I have reviewed the complexities related to this and the areas where we need to learn more. There is no doubt that, in the future, we will have information which will help us to more specifically treat patients for problems related to injury, infection, ICU problems and organ failure. As we do this more patients may survive only to develop complications. Thus, the frequency and mortality of multiple organ failure may stay the same.

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SCORING SYSTEMS

An Overview to Introduce Prognostic Indexes in MODS

A.E. BAUE

Predictions are trickly
particularly about the future.
Sam Goldwyn
Hollywood, CA

Our purpose in this symposium is to seek a consensus on scoring or to try to develop a methodology or system of outcome prediction which could be used by all – a universal scoring system. Such a system could be inter-active and help evaluate therapeutic interventions. Can we all speak the same language? The ground work for this meeting was laid in 1995 here in Trieste when Professors Gullo, Vincent and I reviewed the prognostic indexes and the newly developed sepsis-related organ failure assessment (SOFA) program [1].

There have been several regional conferences on predicting outcome. One of these was the 2nd European Consensus Conference in Intensive Care Medicine in 1993 entitled "Predicting Outcome in ICU patients" [2, 3]*. The questions raised at this conference were as follows:

1. How should outcome of intensive care be defined and assessed?
2. How accurately can we measure severity of illness in ICU patients?
3. Can the various means of measuring illness severity be used in the ICU to predict outcome in groups of patients and in individual cases?
4. What are the human and economic costs of treating patients in the ICU who have a very high risk of death or severe disability?
5. In clinical practice, can the measurement of illness severity be used to provide appropriate and avoid useless intensive therapy?

Three scoring systems were reviewed: Apache III [4], SAPS [5] and MPM-O and 24 [6]. As nearly as I can tell, no consensus was reached other than to keep working. Recommendations included doing research on quality of life after discharge, examination of the decision making process and maintaining medical control of clinical decisions. Illness severity scores were not recommended for

* The first consensus conference dealt with selective decontamination of the gut

routine clinical decision making or for triage. The conference concluded that Severity Scores can be valuable for predicting mortality and for clinical trials. The current low sensitivity of the scores precludes their use for predicting outcome in individual patients.

Wright et al. in a recent publication on "Measurement in Surgical Clinical Research" describe the issues involved in measurement and the development of an index [7]. First is the definition of the purpose of the index. Feinstein classified four different objectives or purposes [8]: 1) to evaluate patients at a single point in time (Status Indexes); 2) measurement of clinical change (Change Indexes); 3) prediction of an outcome (Prognostic Indexes); and, 4) description of clinical change (Clinical Guidelines). Second is the focus or areas of interest of the index. The focus can be objective outcomes, subjective evaluations or generic health status measurements. Third is the type of measurement or Multi-item Indexes. This is followed by scale development for item generation and item reduction. After the instrument has been developed, it must be evaluated. Wright et al. describe the evaluation criteria as sensibility, reliability, validity and responsiveness. Feinstein defined sensibility as "a mixture of ordinary common sense plus a reasonable knowledge of pathophysiology and clinical reality". Reliability means that the same result is obtained when the same phenomenon is measured repeatedly by the same or different physicians. Validity means that the measure represents what is being sought. This can be criterion or construct validity. Finally responsiveness is the ability to measure clinical change. It has also been called sensitivity.

It is helpful to review first where we have been. The history of scoring begins with man's attempts to quantitate his activities (Table 1). Indices or scores have been developed for the status of a situation at a point in time, indices of change, prognostic indices and for clinical guidelines. Scoring systems have been developed for a number of health related matters (Table 2).

After the initial description of MOF [9] a number of excellent classifications of MOF were developed. It was soon recognized by Knaus and his group that there is a wide distribution of severity of illness in patients with similar organ failure classifications [10]. Thus MOF scales were imprecise. There could be a little or a lot of organ failure. Certain combinations of organ failures are more lethal than others [11]. This led to the development of the Apache concept on one hand [12] and the SIRS, MODS, approach on the other [13].

What is the purpose of a score? Why score? What are the issues – to predict an outcome (measure prognosis), describe or classify the severity of illness, to set criteria for clinical trials of new therapies, to assist, guide or stop therapy? Will these improve care? Are the various programs interactive for therapy? Can a worsening score allow one to stop therapy or organ support or an improved score indicate survival? We can describe metabolic and cardioventilatory characteristics which are consistent with illness or survival, but will they contribute to clinical research and other trials. As we compare survival or death and continuity of care – probability may not be a certainty. Finally should we strive for

consensus and a single universal scoring system? Can we ever all speak the same language?

For each area of medical activity many different scores have been developed. Thus for sepsis there are at least 16 different scoring systems (Table 3). For severity of illness scoring there are a multitude of systems (Table 4). To attempt to document the severity of injury and compare trauma results, at least 19

Table 1. History of scoring

Game scores	MOF scores
Romantic conquest by women and men	Disease scores
Wellness scores	Injury scores
Neonatal score - APGAR	TISS-28
Sepsis scores	TRISS - Trauma and Injury Severity Score
SIRS and MODS scores	PISS - Predicted Injury Severity Score
TISS-76 - Therapeutic Intervention Scoring System	

Table 2. Scoring systems

Health Status Evaluation
Severity of Illness
Sepsis
Injury Severity
Futility
Injured extremity

Table 3. Sepsis scoring

Sepsis Severity Score (SSS) - Stevens
Sepsis Score - Elebute - Stoner
Complete Septic Shock Score
Simplified Septic Shock Score
Sepsis Related Mortality Score
Risk of Operative Site Infection Formula
Surgical Stratification System for Intra-Abdominal Infections
Peritonitis Index
DTH - Delayed Hypersensitivity Skin Test Score
LPS - Cytokine Score - LPS - IL - 1B, IL-6
SSS - Severity of Surgical Sepsis
SOFA - Sepsis Related Organ Dysfunction and/or Infection Model
Customized Probability Model
ODIN Model - Organ Dysfunction and/or Infection Model
Mannheim Peritonitis Score - MPS
Baltimore Sepsis Scale - BSS
Systemic Mediator - Associated Response Test - SMART

methodologies have been proposed (Table 5). There are at least ten scoring systems for the evaluation of general health status (Table 6). Even injured extremities have been scored (Table 7), and attempts are being made to develop a futility score (Table 8).

Table 4. Severity of illness scoring

APGAR Score	
APACHE I, II, III	Acute Physiology and Chronic Health Evaluation System
SAPS I, II	Simplified Acute Physiology Score
LODS	The Logistic Organ Dysfunction System
MPM II	Mortality Probability or Prediction Model (System 24, 48, 72)
MODS Score	Multi-Organ Dysfunction Score
CARE	Clinical Assessment, Research and Education System
CIRS	Cumulative Index Rating Scale
PODS	Probability of Death Score
MUM	Multiattribute Utility Model
DPE	Daily Prognostic Estimates
MOF Scoring	Multiple Organ Failure Scoring
OSF	Organ Systems Failure
MSOF Score	Multiple System Organ Failure Score
The Parsonet Score	
CIS	Cell Injury Score of Hirasawa
HIS	Hanover Intensive Score
Physiologic State Classification	Siegel
HPI	Hospital Prognostic Index
TISS	Therapeutic Intervention Scoring System 76 Items
SCOUT	Surgical Complication Outcome Score
New Intermediate TISS	
Simplified TISS	28 Items
PNI	Prognostic Nutritional Index
EPI	Endocrine Prognostic Index
PRISM	Pediatric Risk of Mortality
POPCS	Pediatric Overall Performance Category Score
PCPC	Pediatric Cerebral Performance Category
Murray Lung Injury Score	
MISGS	Medical Illness Severity Grouping System
CCSS	Critical Care Scoring System
POSSUM	The physiological and operative severity score for the enumeration of mortality (and morbidity)
SMART	Systemic Mediator - Associated Response Test
HCWPS	Health Care Workers Predictors of Survival
TICS	The ICU Coma Score
Childs-Turcotte Classification	Liver Disease
Ranson's Criteria	Pancreatitis
Forrester's Classification	MIS
VS	Ventilator Score
AOSFSS	Acute Organ System Failure Scoring System

I have not attempted to provide references for each of these efforts. The major programs will be cited and include: Apache II and III [4, 14], a simplified

Table 5. Injury severity scoring

ISS	Injury Severity Score
AIS	Abbreviated Injury Score
TI	Triage Index
AL	Anatomic Index - HICSDA-8 Code
PEPL	Penetrating and Blunt Injury Code
ASCOT	A Severity Characterization of Trauma
OIS	Organ Injury Scales - for each organ and region
GCS	Glasgow Coma Score
TS	Trauma Score
PTS	Polytrauma Score
TI	Trauma Index
BI	Burn Index
MTO	Major Trauma Outcome Study
HTI	Hospital Trauma Index
CRAMS	Circulation, Respiration, Abdomen, Motor, Speech
MESS	Mangled Extremity Score
ATI	Abdominal Trauma Index
TRISS	Trauma and Injury Severity Score
TNN	The Neural Network
ISS	Injury Impairment Score
FCI	Functional Capacity Index

Table 6. Scoring systems for health status evaluation

SIP - Sickness Impact Profile (general health status)
Functional Independence Measure - FIM
The Barthel Activities of Daily Living Scale
Nottingham Health Profile
McMaster Health Index questionnaire
Quality of Well Being Score
MOS (medical outcome study) Health Status Measures MOS SF-20 and MOS SF-36
Medisgroups Classification
Computerized Severity Index
The Cardiac Risk Index

Table 7. Injured extremity scores

MESI	Mangled Extremity Syndrome Index
MESS	Mangled Extremity Severity Score
PSI	Predictive Salvage Index
LSI	Limb Salvage Index

Table 8. Futility score

Any fatal illness with a life expectancy of six months or less
– immune failure - AIDS
– severe single organ failure - not easily supportable
– COPD requiring increasing O_2 at rest and not an operative candidate
– congestive heart failure, recurrent
– cardiomyopathy - not a transplant candidate
– metastatic malignancy, nonresectable multiple lesions brain, lung, liver, bone, post-radiation therapy
– mental status, unresponsiveness - disoriented as to time, place and person
– cerebral vascular disease - dense stroke with inability to care for one's self but not brain dead
– hepatic failure
– progressive MOF
– severe sepsis with any of the preceding
– end stage metabolic muscular disease
– do not resuscitate order - no code
– incapable of independent living with any of the preceding
– Alzheimer's disease
– persistent vegetative state - how long?

Fig. 1. A SOFA is a piece of furniture on which the cartoon character Dagwood Bumstead is lying

Fig. 2. A cartoon of the Tower of Babel with each construction worker speaking a different language (recommending a different scoring system)

acute physiology score (SAPS II) [5], mortality probability models (MPM II) [6, 15, 16], the therapeutic intervention scoring system (TISS) [17], the multiple organ dysfunction score (MODS) [18], developed by Marshall and the sepsis related organ failure assessment score (SOFA) developed by Vincent and colleagues [19, 20]. The emphasis of this group is on ideal variables which are objective, simple-easily available and reliable, obtained routinely and regularly in every institution, specific for the function of the organ considered, a continuous variable, independent of the type of patients, independent of the therapeutic interventions. The expression SOFA is an interesting one. To those from the United States, SOFA means a couch or a piece of furniture to sit or lie upon (Fig. 1).

Recently LeGall and his group have developed two new instruments for probability determination. The first approach is to customize existing models such as SAPS II or MPM II [24] for subgroups of patients such as those with early severe sepsis [21]. They propose this technique as an adjunct for clinical trials of new therapeutic agents. More recently LeGall et al. for the ICU scoring group have developed a new way to assess organ dysfunction in the ICU. They call this the Logistic Organ Dysfunction System (LODS). On the first day in the ICU they identify from 1 to 3 levels of organ dysfunction for 6 organ systems and the relative severity among organ systems. Most of these programs will be described by their developers later.

There have been a number of studies and publications of comparisons of many of these scoring systems. These include a guide to prognostic scoring systems by Seneff and Knaus [23]. Castella et al. led a multicenter, multinational study and concluded that Apache III, SAPS II and MPM II perform better than

their predecessors and all three showed good discrimination and calibration [24]. Roumen et al. compared seven scoring systems including Apache II and the Injury Severity Score in severely traumatized patients [25]. They concluded that the ISS for example predicted complications such as ARDS and MOF whereas Apache predicted mortality. Barie et al. found that the combined use of Apache III and the MODS score predicted a prolonged stay in the ICU, but could not predict outcome adequately in individual patients [26]. Rutledge raises the question as to whether the ISS will differentiate between severe injury or poor care [27]. Lewis points out that timing of the measurement will make a difference [28]. Comparison of APACHE II and TRIS scores in trauma patients indicated that both accurately predicted group mortality in ICU-trauma patients, but neither was accurate enough for prediction of outcome in individual patients [29].

Recently the problem of medical futility in ICU care has been described. When is medical care and organ support no longer helpful? Civetta has defined medical futility as "a situation in which further therapy seems useless" [30]. Attempts are being made to further define this and also to place such a concept in an ethical setting in the ICU [31-33]. Much more will be heard about this in the future. Knaus and others have reviewed the matter of whether objective estimates of chances for survival should influence therapy to treat or withdraw treatment [34]. As Knaus and his co-workers have stated "probability models can never predict whether a patient will live or die with 100% accuracy" [23]. An exciting area of study will be whether predicted risk of mortality can help to evaluate therapy. Many recent clinical trials of new therapeutic agents have been negative. Initial retrospective evaluations by predicted risk have been encouraging [35].

So where does all of this leave us? How precise do we wish to be? We are better at words and scores (personal classifications, descriptions and calculated constructs) than we are at therapeutic advances which require development, trial and proof. The cost of such programs must also be considered. Will we ever develop a consensus and a single or several systems for universal use? I think not. Even within the last year, new systems have been developed so that one can predict that this will continue. I used the comparison of the message about the Tower of Babel from the Book of Genesis in the Old Testament of the Bible. In that story, God punished mankind by confounding the single language of the people into many languages so that they could no longer understand each other. Work on building a tower to heaven thus ceased (Fig. 2). As LeGall wrote recently "New systems to assess dysfunction are proposed almost every year, and each system differs from the others in large or small ways" [22].

Will we ever develop a scoring system which is accurate enough for individual patients so as to predict mortality with complete certainty. I doubt it, but it is dangerous to make absolute predictions. The vagaries and complexities of human disease are a source of continuous wonderment.

I could also use the evolution of terms for human illness and causes of morbidity and mortality as an example. We began with terms such as infection.

Then sepsis and the sepsis syndrome were developed. The concept of multiple organ failure was developed with scoring systems for it. Then the expression systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) were developed, and everyone hopped on that bandwagon. Bone has now extended the acronymic battle to include the terms CARS (compensatory anti-inflammatory response syndrome), MARS (mixed antagonistic response syndrome) and CHAOS (cardiovascular compromise, homeostasis, apoptosis, organ dysfunction, suppression of immune system). Where will it end? The answer is that it will not end – ever. Man's need to strive and innovate was well described by the poet Ralph Waldo Emerson in "For an Autograph" where he wrote: "Though old the thought and oft expressed tis his at last who says it best". Perhaps we should paraphrase Emerson to read "Tis his at last who says it last".

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Multiple Organ Dysfunction (MOD) Score

J.C. MARSHALL

Articulation of the concept of multiple organ failure some two decades ago [1] marked a seminal shift in our understanding of the process of care in the ICU. Baue's landmark editorial made explicit an evolving recognition, that despite the heterogeneity of conditions that lead to ICU admission, the subsequent clinical course and postmortem findings are remarkably similar. Moreover, death, when it occurs, is not the consequence of isolated lung, heart, or renal failure, but rather reflects the necessary interdependence of multiple organ systems involved in the maintenance of homeostasis.

Two features of this new syndrome were readily apparent. First, it was commonly [2, 3], though not invariably [4, 5], a consequence of occult unrecognized infection. Secondly, it portended significant morbidity and substantial mortality [6].

These two faces of multiple organ failure – one a manifestation of a pathophysiologic process, and the other an expression of ICU morbidity – remain the cardinal features of the clinical syndrome that must be reflected in any system that seeks to describe organ dysfunction. Since organ dysfunction is a potentially preventable complication of critical illness, and in particular of the sequelae of infection, ischemia, and injury, it is particularly desirable that reliable and validated measures of organ dysfunction be developed and tested.

Following the 1991 Consensus Conference of the ACCP/SCCM [7], and based on previous work by Goris [8] and ourselves [5], we developed the Multiple Organ Dysfunction (MOD) Score as an objective tool to quantify organ dysfunction as an outcome in critical illness [9] (Table 1).

Methodologic principles of the MOD score

The MOD Score was developed using a formal methodologic approach to maximize construct, content, and criterion validity.

Construct validity concerns the extent to which the score reflects organ dysfunction as it is seen by the intensivist. To maximize construct validity, we undertook a systemic evaluation of 30 published reports of organ failure to define what systems and what variables would seem to comprise the syndrome [10].

Table 1. The multiple organ dysfunction (MOD) score

Organ system	0	1	2	3	4
Respiratory [a] (PO_2/FIO_2 ratio)	> 300	226-300	151-225	76-150	≤ 75
Renal [b] (serum creatinine)	≤ 100	101-200	201-350	351-500	> 500
Hepatic [c] (serum bilirubin)	≤ 20	21-60	61-120	121-240	> 240
Cardiovascular [d] (R/P ratio)	≤ 10.0	10.1-15.0	15.1-20.0	20.1-30.0	> 30.0
Hematologic [e] (platelet count)	> 120	81-120	51-80	21-50	≤ 20
Neurologic [f] (Glasgow Coma Score)	15	13-14	10-12	7-9	≤ 6

[a] The PO_2/FIO_2 ratio is calculated without reference to the use or mode of mechanical ventilation, and without reference to the use or level of PEEP

[b] The serum creatinine level is measured in mmol/liter, without reference to the use of dialysis

[c] The serum bilirubin level is measured in mmol/liter

[d] The R/P ratio is calculated as the product of the heart rate and right atrial (central venous) pressure, divided by the mean arterial pressure:

$$\text{R/P ratio} = \frac{\text{Heart rate x RAP}}{\text{mean BP}}$$

[e] The platelet count is measured in platelets/mL 10-3

[f] The Glasgow Coma Score is preferably calculated by the patient's nurse, and is scored conservatively (for the patient receiving sedation or muscle relaxants, normal function is assumed unless there is evidence of intrinsically altered mentation)

Content validity reflects the extend to which the score encompasses the nature of dysfunction in any given system. To maximize content validity, we established a series of criteria to define the ideal descriptor of organ system dysfunction and measured candidate variables against these [10]. Finally, *criterion validity* reflects the extent to which the score reflects the process of organ failure when measured by an independent gold standard. Lacking a definable biochemical marker, we chose to use ICU mortality as the standard against which to evaluate criterion validity. ICU rather than hospital mortality was selected since the purpose of developing the score was not to permit the prediction of ultimate survival, but rather to characterize a process whose expression occurs in the ICU and necessitates ongoing care there.

The MOD score is summarized in Table 1. It is similar to the recently published systems including the SOFA Score [11], LOD Score [12], and Brussels' Score [13]. Its differences reflect the conceptual challenges that remain to be resolved if a single widely accepted system is to be developed.

Organ dysfunction scales: unresolved questions

Should a scale reflect deranged physiology or therapeutic intervention?

In seeking to produce a score derived purely from physiologic measures, we have consciously stayed away from any consideration of therapy. Values for

each of the variables are recorded without consideration of therapeutic intervention (the PO_2/FIO_2 ratio, for example, is calculated independent of the presence of mechanical ventilation). This decision was made for several reasons. First we wished to minimize the systematic error that would result because therapy differs from one centre to the next; such an approach maximizes the generalizability of the score. Our purpose in developing the score was to produce a tool that could be used to understand the pathophysiology of the multiple organ dysfunction syndrome, therefore measures reflecting physiology were used in preference to those reflecting therapeutic approach. Physiologic measures are more readily treated as continuous variables, thus increasing the sensitivity of the score. Finally, modelling on our original database showed the effects of incorporating therapy on variable waiting to be minimal. Perhaps this is not surprising. Evidence of inadequate oxygenation, for example, will generally lead the intensivist to initiate ventilatory support to optimize the clinical situation.

When should variables be measured?

The model of organ dysfunction reflected in the MOD Score is one that views organ dysfunction not as an acute and easily reversible abnormality, but as the derangement that remains after maximal support has been instituted. Thus, a patient with hypotension that responded rapidly to volume replacement would not be seen as having cardiovascular dysfunction, whereas another who is normotensive only with maximal volume resuscitation and the use of vasopressors would be considered to have significant cardiovascular dysfunction. Thus determination of the score should occur after, not prior to or during, resuscitation.

Equally such a model of stable dysfunction requires that the measurement of each variable reflect a value that is representative of physiologic derangement over time, to minimize the likelihood that abnormalities of respiratory function, for example, reflect an acute reversible event such as desaturation during suctioning. Thus, the variables recorded to calculate MOD scores are representative values taken at a standard time of day rather than the worst values recorded during a 24 hour period. Recording representative variables further minimizes the bias that results because the frequency of ascertainment varies from one centre to the next. Other approaches to identifying representative variables are logistically complex and were rejected for this reason.

How are variables selected and calibrated?

Unlike a prognostic score that is calibrated to maximize predictive ability, the MOD Score was developed as an outcome measure. Thus, the variables chosen and their weightings were selected not on the basis of their ability to *predict* death, but on the basis of their ability to *describe* organ dysfunction in a clinically relevant manner. Indeed if one accepts the estimate that 20% of ICU

deaths result from processes other than organ dysfunction [14], a valid organ dysfunction measure should record a low score for patients who die without significant organ failure, and thus perform significantly less well as a predictor of ICU mortality.

How is cardiovascular dysfunction measured?

Perhaps the most striking difference between contemporary organ dysfunction scores is in the variable selected to measure cardiovascular dysfunction. Our review of published descriptive systems failed to identify an available marker that met minimally acceptable criteria for incorporation into the MOD Score [10]. Therefore, we developed a novel descriptor termed the Pressure Adjusted Heart Rate (PAR). The Pressure Adjusted Heart Rate is calculated as the product of the heart rate, and the ratio of CVP to mean arterial pressure:

$$PAR = \frac{HR \times CVP}{MAP}$$

Like the PO_2/FIO_2 ratio, the PAR provides a measure of physiology that is less dependent on therapy. Prior to volume replacement, the value is low; as the CVP rises, the PAR increases. A normal physiologic response – a reduction in heart rate as the mean arterial pressure increases – will keep values of the PAR low. On the other hand, persistent tachycardia and hypotension despite adequate filling pressures produce high values. Moreover, tachycardia resulting from vasoactive drugs will likewise increase the value of the PAR.

A major drawback of the PAR is that it has not been widely validated. It may well be that other simpler and equally valid measures of cardiovascular dysfunction (for example, fluid balance or change in body weight) can be identified. We are currently undertaking a prospective evaluation of the performance of the PAR and several other candidate variables for the description of cardiovascular dysfunction in hopes of identifying an optimal descriptive valuable.

Applications of the MOD score

A validated tool to measure organ dysfunction has a number of potential uses both within the framework of clinical trials and in day to day ICU practise. These will be briefly outlined.

Prognostication and severity of illness stratification

Calculated at the time of ICU admission, an organ dysfunction scale provides a measure of global illness severity, expressed using the construct of the multiple

organ dysfunction syndrome. Although we found that the performance of the MOD Score was comparable to that of APACHE II in predicting ICU outcome [9], in general it would be expected that an organ dysfunction score will not be as robust in predicting the probability of ICU survival. On the other hand, for a clinical trial that uses organ dysfunction as an endpoint, such a score provides both a potential stratification variable and a means of ensuring comparability of study groups at the outset of the study.

Organ dysfunction as a point measure of illness severity

Organ dysfunction scores calculated on any given day of the ICU stay provide a point measure of severity of illness and, by inference, of the intensity of therapeutic intervention. Thus, daily organ dysfunction scores can serve the same role currently played by instruments such as the therapeutic intervention scoring system that measure therapeutic intensity.

Measurement of global severity of organ dysfunction

By summing the worst values for each individual variable over the entire ICU stay, an organ dysfunction score provides a measure of the global severity of illness over time. Such a measure incorporates not only pretreatment derangements, but also those that develop during the ICU stay and has been the most widely used approach to the measurement of organ failure.

Measurement of attributable ICU morbidity

Of greater interest in evaluating an ICU therapy is the ability to measure attributable morbidity during the ICU stay. Using the MOD Score, this can be accomplished by calculating a ΔMODS – the difference between the overall MOD Score and the MOD score on the day of admission. This difference represents organ dysfunction developing following ICU admission and therefore potentially amenable to modulation by ICU-based therapy. The ΔMODS can be calculated over the entire ICU stay or over a defined time interval, such as the 28 day period of a clinical trial.

Combined measures of morbidity and mortality

A composite measure that includes both morbidity and mortality is the Mortality-Adjusted MOD Score. Since survival with a high MOD Score is clearly preferable to death with a low Score, all nonsurviving patients are automatically assigned a maximal number of points, 24. For surviving patients, the number of points scored is the number of points accumulated over the ICU stay. Such a calculation converts the dichotomous variable of mortality into the maximum

value of a continuous scale and therefore permits combined evaluation of morbidity and mortality.

Conclusions

A number of similar systems have evolved for the quantification of organ dysfunction in critical illness. Their differences reflect both different concepts of the nature of the syndrome and different potential uses. Nonetheless, their similarities are striking and it is to be anticipated that consensus on a single, widely applicable model will ultimately be achieved.

Perhaps one of the most important differences between existing systems is their implicit intent in measuring pathophysiologic derangements of a disease process on the one hand, and the therapy required to support these on the other. While pathophysiology and therapy are intimately interrelated, it may well be useful to evaluate each separately within a clinical trial. A purely physiologic measure such as the MOD Score may have advantages in describing a disease process and elucidating details of its epidemiology and fundamental biology. As a continuous variable, it is sensitive, and because it avoids therapy, it avoids the bias that would result from differing therapeutic practises.

On the other hand, the dichotomous decision to institute therapy or not reflects the fundamental reality of ICU care from the perspective of the intensivist. Therefore, a scale based on a series of dichotomous, therapy-dependent variables reflecting these decisions may be intuitively more appealing to the practitioner. Moreover, since the institution of therapy carries inevitable costs, a therapy-based measure may provide a better reflection of the impact of a novel therapy. Thus, it may well be desirable to look to developing two complementary systems – one based in physiology and similar to the MOD Score, and a second reflecting a series of dichotomous therapeutic valuables.

The task of achieving consensus on the description and quantification of organ dysfunction in critical illness is much more than a question of the simple promotion of competing models. Whether organ dysfunction represents a single disease process for which therapeutic intervention may be beneficial is unknown. However it is clear that this process, however imperfectively defined, is a leading cause of morbidity and mortality in the ICU and responsible for significant demands on national health care budgets. As a generic measure of ICU morbidity, the model of organ dysfunction provides a useful framework for quantifying the adverse consequences of therapy. The need to do so in a valid and methodologically rigorous fashion is compelling.

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The Logistic Organ Dysfunction (LOD) System

J.R. LE GALL, J. KLAR, S. LEMESHOW

The assessment of the severity of organ dysfunction in the ICU is a critical tool for conducting clinical trials, especially sepsis trials. The evaluation of new therapies cannot be successfully achieved without checking the degree of organ dysfunction. It is not adequate to assess severity, or to describe a patient's condition, by simply counting the number of dysfunctioning organ systems.

In fact, new systems to assess organ dysfunction are proposed almost every year, and each system differs from the others to a greater or lesser extent. As early as 1980, Fry et al. proposed a system of 4 organ failures for surgical patients: pulmonary, hepatic, gastrointestinal, and renal failure [1]. In 1983, Stevens described the Sepsis Severity Score comprising 7 failures, each with 5 severity levels [2]. The system of Marshall et al. contained metabolic failure and took anergy into account [3]. The widely used Organ System Failure (OSF) score was published in 1983 by Knaus et al. [4], and in 1989 [5] hepatic failure was added. Fagon et al. added infection to the assessment of organ dysfunction and called their system ODIN (Organ Dysfunction and/or Infection) [6]. Hebert et al. published a multiple organ failure scoring system for patients who have sepsis syndrome [7]. Recently, Marshall et al. proposed the Multiple Organ Dysfunction Score (MODS) based on a review of 30 reports in the literature [8].

In many scoring systems, each organ dysfunction is graded from 1 to 4 points, or from 1 to 6 points, and a score is produced by adding the points. These systems cannot adequately reflect patient severity. Not only are the ranges defining the levels different from those found using statistical methods, but weighting each organ system in the same way does not take into account the differential prognostic significance of the involved organs.

In order to propose an objective system, we decided to use the large data base of the European North American study (ENAS) and apply the statistical technique of multiple logistic regression [9-11]. Although based on sophisticated statistical methods, our goal was to develop a system that was as simple as possible to apply in the ICU. In developing a statistically based system, ranges and weights of the variables defining levels of organ dysfunction can be determined objectively, the significance of severity levels for each organ can be iden-

tified, and the levels of dysfunction can be weighted according to their relative prognostic significance.

In the resulting Logistic Organ Dysfunction (LOD) System, the points for individual severity levels of each organ system reflect both the relative severity of the levels within an organ system and the relative severity of the levels among organ systems. The LOD score is a global score that can be calculated to summarize the combined effect of dysfunction among several organs. In addition, the LOD model is a logistic regression equation that can be used to translate the score into a probability of mortality based on organ dysfunctions.

How was the LOD system created?

Data on 14,745 consecutive ICU admissions were collected in 137 medical, surgical, or mixed ICUs in 12 countries on consecutive admissions to the ICUs [12]. Eligible patients were aged 18 years or older; burn patients, coronary care patients, and cardiac surgery patients were excluded. To develop and validate the LOD System, 80% of the patients in the database were randomly selected to constitute the developmental sample, and the remaining 20% composed the validation sample.

Variables were extracted from the database to define failure, based on a combination of 12 variables, for six organ systems: cardiovascular (heart rate and systolic blood pressure), hematologic (platelets and white blood cell count), hepatic (bilirubin and prothrombin time), neurologic (Glasgow Coma Score), pulmonary (ventilation/CPAP [continuous positive airway pressure] status and PaO_2/FiO_2 ratio), and renal (creatinine, urea, and urine output). The variables had been recorded as the worst value in the first 24-hour period in the ICU.

For sedated patients, the GCS was ascertained either from interviewing the physician who ordered the sedation, or by reviewing the patient's medical record before sedation. If a variable was not measured for a patient, it was assumed to be within the range of normal. All variables except platelet counts and prothrombin time (PT) were continuously scaled. Platelet counts were recorded as being less than 50×10^9/L, and PT was recorded as being more than 3 seconds over standard or less than 25% of standard.

The analysis was designed to first identify cut points that defined variable ranges associated with changes in mortality rate.

When the points for each severity level were known, the LOD Score was calculated by summing the points associated with each of the involved organ systems. The LOD score was then used as the single variable in a multiple logistic regression equation of the form:

$$\text{Logit} = \beta_0 + \beta_1 \times (\text{LOD Score})$$

The logit containing the LOD Score was then converted to a probability of hospital mortality as:

$$\Pr(Y = 1/\text{logit}) = \frac{e^{\text{logit}}}{1 + e^{\text{logit}}}$$

where Y equaled 1 for patients who died, Y equaled 0 for patients who lived, Pr indicated probability, and e indicated a mathematical constant 2.7182818, which represented the base of the natural logarithm.

The assessment of model performance was the final stage of the analysis. To evaluate model calibration, Hosmer-Lemeshow goodness-of-Fit tests, comparing observed with expected mortality, were performed [3]. To evaluate discrimination, area under the receiver operating characteristic (ROC) curve was calculated [13].

The LOD points that can be scored for each level of organ dysfunction are shown for each organ system in Table 1. From the Table, it can be seen the neurologic, cardiovascular, and renal dysfunction score the maximum of 5 LOD points for the most severe level of dysfunction. Pulmonary and hematologic system dysfunction score a maximum of 3 LOD points, and hepatic dysfunction scores a maximum of 1 LOD point. The LOD score can range from 0 to 22 points. Figure 1 shows the distribution of the LOD score from 0 to 22 points in the developmental sample. An LOD score of 0 indicates no organ dysfunction. An LOD score of 1 is the score for the lowest level of severity for 1 organ system dysfunction, and an LOD score of 22 points is the score for the highest level of severity for all 6 organ dysfunctions.

Of the 10,547 patients in the developmental sample, 1293 (12,3%) had no organs dysfunction, 2723 (25,8%) had 1 organ dysfunction, 2615 (24,8%) had 2 organs in dysfunction, and 3916 (37,1%) had 3 or more organs in dysfunction.

Regardless of the number of organs in dysfunction, the LOD score varied widely by the severity of the dysfunction. Depending on the involved organs

Table 1. The logistic organ dysfunction (LOD) system: Three levels of increasing severity with corresponding points for each organ system

Organ System	Severity Level			
	0	**1**	**2**	**3**
	LOD Points			
Neurologic	0	1	3	5
Cardiovascular	0	1	3	5
Renal	0	1	3	5
Pulmonary	0	1	3	...
Hematologic	0	1	3	...
Hepatic	0	1	...	...

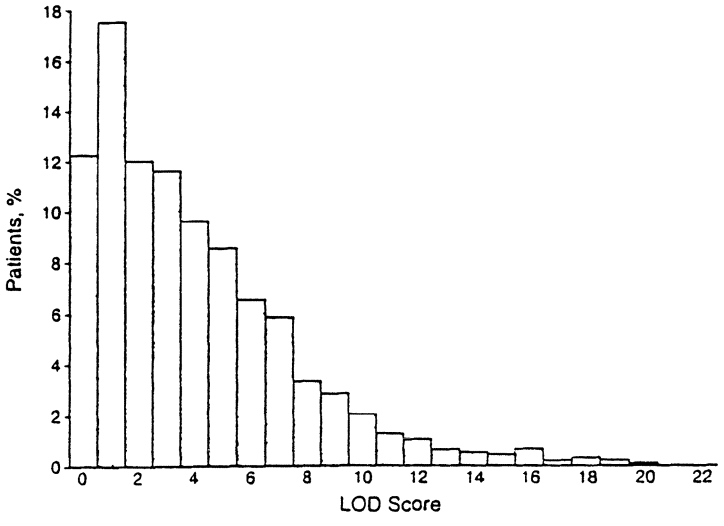

Fig. 1. Distribution of the logistic organ dysfunction (LOD) score among 10,547 patients in the developmental sample

and the level of severity, the LOD score can be as low as 1 or as high as 5 with 1 organ dysfunction.

It can be as low as 6 or as high as 22 with 6 organs in dysfunction.

The final scoring system for the LOD score is presented in Table 2. For each organ dysfunction defined by more than 1 variable, only one of the variables needs to be in the abnormal range for the LOD points to be assigned. All of the variables defining an organ dysfunction must be within the normal range to receive 0 LOD points for that organ dysfunction (Table 3). To calculate the LOD score for a patient, the points for each organ dysfunction are summed.

The application of the LOD score in the ICU can be illustrated using data for a hypothetical patient as an example. Consider a patient admitted to the ICU for septic shock with extreme oliguria. The WBC count is 2.0 x 10^9/L, the systolic blood pressure is 60 mmHg, and there is no evidence of pulmonary, hepatic, or neurologic dysfunction. The creatinine level is 88 μmol/L (1 mg/dL).

In calculating the LOD score, being oliguric contributes 5 points to the LOD score for renal dysfunction, the low WBC count contributes 1 LOD point for hematologic dysfunction, and the systolic blood pressure contributes 3 LOD points for cardiovascular dysfunction, for a total LOD score of 9 points.

Table 2. Scoring for the logistic organ dysfunction (LOD) system

Organ System Measures	LOD Points						
	Increasing Severity/Decreasing Values			Organ Dysfunction Free	Increasing Severity/Increasing Values		
	5	3	1	0	1	3	5
Neurologic							
Glasgow Coma Score	3-5	6-8	9-13	14-15	≥ 6	...	...
Cardiovascular							
Heart rate, beats/min	< 30	...	...	30-139	≥ 140	...	...
or				and	or		
Systolic blood pressure, mmHg	< 40	40-69	70-89	90-239	240-269	≥ 270	...
Renal							
Serum urea, mmol/L (g/L)	...	...	...	< 6 (< 0.36)	6-9.9 (0.36-0.59)	10-19.9 (0.60-1.19)	≥ 20 (≥ 120)
or							
Serum urea nitrogen, mmol/L (mg/dL)	...	...	...	< 6 (< 17)	6-9.9 (17-< 28)	10-19.9 (28-<5 6)	≥ 20 (≥ 56)
				and	or	or	
Creatinine, μmol/L (mgL/dL)	...	...	...	< 106 (< 1.20)	106-140 (1.20-1.59)	[3]141 ([3]1.60)	...
				and		or	
Urine output, L/d	< 0.5	0.5-0.74	...	0.75-9.99	...	≥ 10	...
Pulmonary							
PaO_2 (mmHg) FIO_2 on MV or CPAP		< 150	≥ 150	No ventilation no CPAP	...	...	...
(PaO_2[kPa]/FIO_2)		(<19.9)	([3]19.9)	no IPAP	...	...	...
Hematologic							
White blood cell count, x 10^9/L	...	< 1.0	1.0-2.4	2.5-49.9	≥ 50.0	...	...
			or	and			
Platelets, x 10^9/L	...	...	< 50	≥ 50			
Hepatic							
Bilirubin μmol/L (mg/dL)	...	...	...	< 34.2 (< 2.0)	≥ 34.2 (≥ 2.0)	...	...
				and	or		
Prothrombin time, s above standard (% of standard)	...	...	(< 25%)	≤ 3 (≥ 25%)	> 3	...	...

Table 3. Variables and definitions for the logistic organ dysfunction (LOD) system

All variables must be measured at least once. If they are not measured, they are assumed to be within the normal range for scoring purposes. If they are measured more than once in the first 24 h, the most severe value is used in calculating the score.

Neurologic System

Glasgow Coma Score: Use the lowest value; if the patient is sedated, the estimated Glasgow Coma Score is 14 or 15.

Cardiovascular System

Heart rate: Use the worst value in 24 h, either low or high heart rate; if it varied from cardiac arrest (5 LOD points) to extreme tachycardia (3 LOD points), assign 5 LOD points.

Systolic blood pressure: Use the same method as for heart rate (e.g., if it varied from 60 to 250 mmHg, assign 3 LOD points). The patient is free of cardiovascular dysfunction if both heart rate and systolic blood pressure are scored with 0 LOD points. This principle is the same for all organ dysfunctions that may be definited by more than 1 variable.

Renal System

Serum urea or serum urea nitrogen level: Use the highest value in mmol/L or g/L for serum urea, in mmol/L (mg/dL) of urea for serum urea nitrogen.

Creatinine: Use the highest value in μmol/L (mg/dL).

Urinary output: If the patient has been in the ICU for less than 24 h, make the calculation for 24 h (e.g., 1 L/8 h = 3 L/24 h).

If the patient is on hemodialysis, use the pretreatment values.

Pulmonary System

If ventilated or under continuous positive airway pressure (CPAP), use the lowest value of the PaO_2/FIO_2 (fraction of inspired oxygen) ratio (whether PaO_2 is mmHg or kPa). A patient who has no ventilation or CPAP during the first day is free of pulmonary dysfunction.

Hematologic System

White blood cell count: Use the worst (high or low) white blood cell count that scores the highest number of points.

Platelets: If there are several values recorded, find the lowest value and assign 1 LOD point if the lowest value is less than 50 x 10^9/L.

Hepatic System

Bilirubin: Use the highest value in μmol/L (mg/dL).

Prothrombin time (seconds or %): If there are several values recorded, assign 1 LOD point if the prothrombin time was ever more than 3 s above standard or less than 25% of standard during the day.

Developing and validating the LOD model

The LOD score was first calculated for each of the 10,547 patients in the developmental sample by summing the points for each organ system based on the recorded levels of each variable included in the system. The LOD score then was used as the only term, along with a constant term, in a new logistic regression equation, resulting in a model that provided an estimate of the severity of organ dysfunction as defined by the probability of hospital mortality.

The equation for the logit was = – 3.4043 + 0.4173 (LOD score).

This logit was the converted to a probability of hospital mortality for each patient:

$$\Pr(y = 1 \text{ logit}) = e^{-3.4043 + 0.4173\,(\text{LODscore})} / 1 + e^{-3.4043 + 0.4173\,(\text{LODscore})}$$

The goodness-of-fit and area under the ROC curve for this model were both excellent in the developmental sample (Table 4), and the validation sample. The probability of hospital mortality for each value of the LOD score is shown in Table 5.

Table 4. Goodness-of-fit of the logistic organ dysfunction (LOD) model among 10,547 patients in the developmental sample

Probability	Survived, No		Example 2	
	Observed	Expected	Observed	Expected
0.00-0.032	51	1251.4	51	41.6
0.032-0.048	1781	1765.0	73	89
0.048-0.071	1172	1184.3	103	90.7
0.071-0.104	1108	1100.1	120	127.8
0.104-0.150	853	866.2	166	152.8
0.150-0.211	733	720.2	180	192.8
0.211-0.382	891	889.9	442	443.2
0.382-0.587	314	319.8	368	362.2
0.587-0.833	131	132.0	388	387.0
0.833-1.000	29	25.1	402	405.9

The steepest increases in the probability of mortality occur for LOD scores from 1 to 32, with an approximative 10% increase in risk for each point increase in the score. For an LOD score of 12 or more, the risk is over 80%; the risk stays high but increase less rapidly as the score increases to the maximum of 22 points, which has an associated probability of mortality of 99.7%. There are several scenarios by which a patient could receive an LOD score of 12 points or more: either by several organs being involved at a moderate to severe level of dysfunction or by the severity level of fewer organs being very high. In any such scenario, the mortality risk is very high. Intermediate risk using the LOD System appears to occur in the range between approximately 5 to 10 points, and there are numerous combinations of organs and severity levels that would result in such a score.

The hypothetical patient described above had an LOD score of 9 points. From Table 5, it can be seen that the probability of hospital mortality for that patient would be 58.7%. While it is obvious that 3 organs were involved, the LOD System weights the severity of dysfunction for the specific organ system and provides a corresponding estimate of the probability of hospital mortality.

Use of the LOD system

The LOD score measures both the importance of the organ system relative to the others and the degree of severity within that system. Most organ dysfunction

systems are scored with the worst severity level for each organ assigned the same number of points, but giving the same number of points for a low GCS (5 LOD points) as for a high bilirubin level (1 LOD point) does not correctly characterize patient's conditions.

Table 5. Conversion of the logistic organ dysfunction (LOD) score to a probability of hospital mortality using the LOD model

LOD Score	Probability of Hospital Mortality, %
0	3.2
1	4.8
2	7.1
3	10.4
4	15.0
5	21.1
6	28.9
7	38.2
8	48.4
9	58.7
10	68.3
11	76.6
12	83.3
13	88.3
14	92.0
15	94.6
16	96.4
17	97.6
18	98.4
19	98.9
20	99.3
21	99.5
22	99.7

Of the 6 organ systems described by the LOD System, neurologic, cardiovascular, and renal dysfunction were the most severe and received the maximum of 5 LOD points for the most severe level of dysfunction. Pulmonary and hematologic dysfunction both received 3 points for the most severe level of dysfunction. Hepatic dysfunction received 1 point. It is notable that Fagon et al. found that cardiovascular, renal, respiratory, and neurologic system dysfunction were the most severe, while hematologic and hepatic system dysfunction were less severe.

The most severe level of neurologic dysfunction, receiving 5 LOD points, was defined by a GCS less than 6. Neurologic dysfunction was measured by the

actual GCS in patients who were not sedated patients. The criteria and weights for neurologic dysfunction proposed for the MODS are somewhat similar to those for the LOD System, although 4 levels of dysfunction are defined rather than 3.

In the LOD System, cardiovascular system dysfunction could also be very severe, with a state of severe shock adding 5 points to the LOD score. Adding therapeutic measures such as the use of vasoactive drugs was not included in the LOD definitions. The LOD score was developed using data from the first ICU day, and the physiological measurements represented patient's conditions prior to therapy. The worst recorded values are those that receive the highest number of LOD points. For example, if at different times on the first ICU days a patient has tachycardia of 150 beats per minute (1 LOD point) and bradycardia of 25 beats per minute (5 LOD points), 5 points are added to the LOD score. After the first ICU day, when a patient is receiving continuous therapy, the problem of scoring cardiovascular variables is, indeed, a difficult one. The variable proposed for the assessment of cardiovascular dysfunction in the MODS is pressure-adjusted heart rate (product of heart rate multiplied by the ratio of the central venous pressure to the mean arterial pressure). This variable depends on resuscitation and the use of blockers and pressors. The central venous pressure is not recorded in all patients, which limits the value of this variable. Although hypertension and bradycardia have not classicly been regarded as part of the multiple organ system syndrome, they nevertheless reflect an abnormality in the functioning of the cardiac system and were associated with a worse outcome than was the case for patients without these factors in our study. This result suggests that previous definitions of early cardiovascular dysfunction need to be modified.

Renal dysfunction, as manifested by low urine output (oliguria) or high serum urea levels, also receives 5 LOD points for the most severe level of dysfunction, which has been noted in other studies of renal dysfunction in intensive care. There is no distinction between chronic and acute renal dysfunction in the LOD scoring, as the focus is on the relevant physiological measurements without having to rely on diagnostic assessments. Again, the decision as to what constitutes the worst value is based on the number of points assigned. For example, if a patient has oliguria of 0,4 L/d (5 LOD points), 5 points are added to the LOD score, regardless of the level of creatinine. To rely only on creatinine could actually postpone the confirmation of renal dysfunction, since it may take several days to observe a rise in creatinine. In several assessment systems, serum creatinine concentration is the only component of renal dysfunction measurement. Serum urea or serum urea nitrogen, as well as daily urinary output, are measured in many countries and have a prognostic weight independent of creatinine. The coefficients for both urea and urinary output demonstrated a stronger association with hospital mortality than the coefficients for creatinine, and when the variables were considered in combination to define renal dysfunction, the association with mortality was even stronger.

Pulmonary dysfunction receives only 3 LOD points for the most severe level. Patients who have been assisted with neither ventilation nor CPAP are considered to be free of pulmonary dysfunction and receive 0 points towards the LOD score. The PAO_2/FiO_2 ratio was also used in the MODS calculations to define levels of pulmonary dysfunction; however, it was not clear whether all of their population of 692 surgical patients were receiving mechanical ventilation, which was not the case for the consecutive admissions that composed the ENAS database.

Hematologic dysfunction also scores a maximum of 3 LOD points, with the most severe level defined by a WBC count less than 1.0×10^9/L. This suggests that a very low WBC count is not as strongly associated with mortality as the most severe levels of dysfunction of other organs, all other things being equal. The data for platelet counts were collected as a binary variable indicating only whether platelet counts were low (less than 50×10^9/L), and this level of measurement resulted in a severity level that receives only 1 LOD point. The MODS uses only platelet counts, measured on a continuous scale, in the assessment of hematologic system dysfunction. Platelet counts less than 50×10^9/L showed a strong association with mortality in that study, consistent with the LOD System categorization.

Hepatic dysfunction scores a maximum of 1 LOD point. This suggests that early hepatic dysfunction by itself is not strongly associated with mortality, but its occurrence in association with the dysfunctioning of the other organ systems worsens the prognosis in an ICU patient. Unlike the MODS, hepatic dysfunction contributed the least to the scoring of multiple organ dysfunction in the LOD System, allowing a maximum of 1 LOD point. Using PT to assess hepatic dysfunction incorporated the measurement of a variable that may be abnormal even when the bilirubin is within normal limits. Since our analysis was restricted to the first 24 hours in the ICU, it would be expected that hepatic dysfunction would be more heavily weighted later in the ICU stay than during the first ICU day. In future LOD research, data for platelet count and PT should be collected as a continuous measurement to confirm whether the current cut points are best suited to reflect the association with mortality.

Although developed using the same database, there are important differences between the SAPSII and the LOD systems. The former takes into account not only several physiologic parameters, but also includes age, the type of patient admission, and several comorbidities. The LOD System was designed to characterize 6 distinct organ systems and uses only physiological measurements to do so. The information from the physiological measurements is grouped in a manner that permits the characterization of organ dysfunction, both as to the number of affected organs and the degree of dysfunction for each organ. In the LOD System, 1 abnormal element is sufficient for the classification of organ dysfuction.

Multiple organ dysfunction is not necessary for the application of the LOD System, as it applies to both single or multiple organ dysfunctions. This makes

the LOD System more broadly applicable, since less than one third of patients in an ICU may have 2 or more organs in dysfunction, with the majority having only 1 organ dysfunction. In our database, which comprised several tertiary care units, 26% of patients had 1 organ dysfunction, and 62% had 2 or more organs in dysfunction. The concept of multiple organ dysfunction implies the involvement of multiple organs, rather than a single organ, but the LOD System grades organ dysfunction in such a way that severity due to organ dysfunction can be quantified, whether 1 to 6 organs are involved. As for the severity scores [15, 16], an objective organ dysfunction system is probably superior to the previous ones.

Conclusion

The proposed LOD System, which was developed using statistical methods that determined the relative weights of the several organ systems and of the levels of severity within each organ system, also produces an estimate of the risk of mortality that demonstrated excellent calibration and discrimination. The LOD System can be used for the assessment of organ dysfunctions developing later in the ICU stay, particularly among elective surgery patients who are often free of organ dysfunction when admitted to the ICU. The large ENAS database from which the system was developed, however, comprised a mix of medical patients, emergency surgical patients, and elective surgical patients who manifested measurable levels of organ dysfunction on the first ICU day. Many of the ICUs in the ENAS database were tertiary care units, and patients entered them at a relatively advanced stage of disease, as reflected by the 62% of patients with 2 or more organs in dysfunction on the first day in the ICU.

Any system to assess organ dysfunction that uses first ICU day variables must be validated for use at other time periods, including the LOD System, and future studies must be designed for that purpose. The validity of the estimate of the probability of mortality from the conversion of the LOD score to a probability using the LOD model on subsequent ICU days has not been tested.

Studies of the association with mortality of an LOD score that is collected daily in the ICU need to be undertaken. Also, further studies that take into account the duration of dysfunction will be needed to estimate the probability of hospital mortality at later points in the ICU stay. Duration of dysfunction is commonly associated with a worsening prognosis, even if a patient's condition is unchanging, since absence of improvement is a negative sign.

Having a tool to quantify the severity of organ dysfunction is necessary in order to evaluate the effectiveness of treatment, not only on mortality but on the resolution of organ dysfunction. Successful resolution of organ dysfunction, however, has not been clearly defined. Some researchers have proposed the number of days free from organ dysfunction as a marker of resolution for an

outcome measure. For such a purpose, the number of days with a zero for the LOD score could be calculated.

As with all models designed for use in a dynamic and changing environment, the LOD System must be kept up-to-date and applicable in the face of changing case mix and ICU therapies. In its present form, the LOD System we have proposed is based on objectively derived coefficients that weight the severity of organ dysfunction differentially both among the 6 organ systems and within each organ system. The results of our analysis by defining the relative association of levels of severity with hospital mortality, suggest that the LOD System has great potential as a tool with which to assess the real severity of organ dysfunction among general medical and surgical ICU patients.

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Will the Use of Scores Benefit the Individual Patient and Improve Therapy?

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Since the introduction of a 10 point scale for newborn infants [1] in 1953 by Apgar numerous scores and scales have been developed in medicine. A score is an attempt to integrate many different information like blood pressure, heart rate or laboratory data into a single one-dimensional numerical value. The more complex a clinical situation is the more efforts are made to develop and refine score systems. Therefore, many scores for patients in the intensive care unit (ICU) have been published.

Scores should help to classify diseases or health states, facilitate comparisons to other cases, or enhance decision-making. Scores are used to predict future events like prognosis or outcome, and economists and administrators use scores to achieve a justifiable reimbursement policy.

The central point of a score system is the reduction and summary of diverse clinical data. The reduction of information can help to concentrate on the essentials, but this reduction naturally causes a loss of information. Many different clinical situations are projected on the same score value. Thus a score is like a pair of glasses giving a selective view of the patient's clinical situation. Regarding an individual patient, this sacrifice of information implies that scores will never replace the underlying data but provide a context allowing interpretation.

In the following paragraphs, clinical situations where scores might have a direct effect on the individual patient are presented. Knowledge about the problems and limitations of score systems is a prerequisite for their application.

Indirect and direct effects in the individual patient

The *indirect benefit* of score systems is widely known and demonstrated in many papers. First of all, research results can be presented much easier and results of clinical trials become more objective and reproducible if scores were used (inclusion criteria, description of patients, assessment of outcome). Second, scores can be used to perform quality audits. The actual outcome in a group of patients can be compared to what is expected in these patients where the expected outcome is based on a severity classification with scores. Third,

dealing with scores undoubtedly has also an educational effect. Especially younger physicians will benefit from these considerations in teaching rounds.

The above mentioned use of scores may indirectly affect patient care by introducing a new therapy or enhancing the level of education. A *direct effect* is present if a therapeutic or diagnostic procedure is induced (or withdrawn, or denied) due to a score value, which would not have been done without this information. Direct effects of scores in intensive care may occur in the following situations:

- triage
- initiation of procedures
- discharge from the ICU
- termination of therapy.

Triage decisions are well-known in catastrophes or in the battlefield where the discrepancy between availability and need of care is usually huge. But similar considerations are sometimes necessary in intensive care. The Society of Critical Care Medicine Ethics Committee defined "triage" as "finding the most appropriate disposition for a patient based on an assessment of the patient's illness and its urgency" [2]. They further state that "priority for admission to an ICU should correlate with the likelihood that ICU care will benefit the patient substantially more than non-ICU care. Patients with poor or very good prognosis should not be admitted" [2]. It is very imaginable that decisions to admit a patient to an ICU or discharge a patient to a normal ward can be supplemented by a severity of illness classification based on scores: "Triage involves a common logic that includes probability estimates of outcome" [2]. On the other hand it is clear as well, that those estimates based on scores will never be the only criterion for admission or discharge policies.

The initiation of certain procedures is a further area where scores might have a direct influence. Murray and coworkers investigated whether provision of computer-based prediction of outcome would alter patient management [3]. 1025 ICU patients, admitted after severe head injury, were studied during three time periods. The probability for survival was calculated. During the baseline phase the outcome estimate was withheld, while nurses and physicians were given this information in the second phase. Phase three was again without prediction in order to evaluate the continuation of behavioural changes. Aspects like intubation and/or ventilation, administration of osmotic agents, or intracranial pressure monitoring were chosen as indicators for possible changes in patient management. They found that the average frequency of use of these procedures was similar or slightly increased in patients with good and moderate prognosis, while there was a substantial decrease of 39% in patients with a poor prognosis (risk of death > 80%). This tendency even continued after the computer prognosis had been withdrawn in phase three. Thus outcome predictions derived from score values might well have a direct influence on the initiation of certain procedures.

Besides the initiation of certain procedures the termination or withdrawal of therapy in critically ill patients is another point of controversial discussion. Intensive care is costly, resources are limited, and the number of patients needing intensive monitoring and therapy increase. But beyond economic considerations it is an ethical question whether it is justified to artificially prolong dying. Technological advances in intensive care can prolong patients' lives but also their suffering. Therefore it is a challenge to identify hopelessly ill patients who will not benefit from further maximal therapy [4]. But how can one identify those patients? Chang et al. published a prediction model based on slightly modified daily Apache II assessment [5, 6]. All patients predicted to die in his test set (n = 112) and validation set (n = 212) actually died so that he had no false positive predictions. The published criteria were subsequently tested by other investigators. Rogers et al. found in 3350 ICU patients that actual mortality rates among patients predicted to die vary between 48% and 69% only (depending on the criterion used) [7]. Our own observations in 1575 ICU patients identified 42 patients predicted to die according to the Chang criteria. 40 of them actually died (95%), but two patients survived.

Score values can give only probability estimations of outcome based on previous observations of many similar cases [8]. A 100% certainty is impossible. Therefore, decisions to withdraw treatment will never be based on a score value alone. The individual situation including the patient's wishes and preferences as well as the expected benefit from further therapy have to be taken into account seriously [2]. The score-based outcome prediction is only one small part in the complex puzzle of the decision process.

Limitations and problems

Any method, including scores, has some inherent limitations. Like positive blood culture results may be due to contamination of the sample, score values can also be misinterpreted. Those who apply scores especially in the individual patient should well know about these problems.

Interpretation

Most severity of disease classification systems like Apache II, SAPS, etc. can be transformed into a risk of death estimate. Applied to an individual patient, this prognosis may cause confusion, especially if a patient with a good prognosis actually dies. A 10% risk of death estimate does not exclude a life-threatening situation. It only means that only one out of ten cases with a similar score value will die. The prognostic information of a score is a probability based on previously observed cases with similar score values. Therefore, the validity of its prognosis can only be tested in a *group* of patients.

Fixed components

A score value usually is composed of several items, identified by experts or statistical procedures, each adding a predefined value to the total sum. For example, a serum potassium below 0.6 mMol/L adds 2 points to the total Apache II score. But in a specific clinical situation a certain derangement may be much more important for survival than suggested by two score points. A scoring system that considers all clinical circumstances would require a rather complex model and would still miss some unforeseen situations. Therefore, a score value will always need a clinical interpretation.

Applicability

A structured collection of data is the first step in the development of a scoring system. Patients with a certain disease or other similar characteristics (e.g. admission to ICU, trauma) are documented, and with statistical methods a formula for a score is derived from the data. The application of that score to new patients will yield most reliable results if these patients are as comparable as possible to the initial group of patients. The use in patients with a different disease as well as in a small subgroup of patients may cause a substantial bias. The Apache II score, for example, was developed in a general ICU population. Its application to trauma patients only causes a well-documented under-estimation of risk of death [9]. But even if patients are comparable, the transfer of a score into a different setting (e.g. in another country) may cause inaccuracy. In general, the application of a score system primordially requires a validation study.

Validy of measurement

A score is only as good as its components. If some measurements are very inaccurate or show a high inter-rate variability, the final score value will have the same shortcomings. A good example is the Glasgow Coma Score (GCS) in intensive care patients. This score was developed by Teasdale and Jennett to describe the severity of a head injury [10]. In these patients it has a high prognostic value. But most ICU patients are intubated and sedated, and a valid assessment of their consciousness is impossible. In this situation, one can a) record the actual state regardless of being influenced by drugs (i.e. 3 points), b) continue to document the last valid measurement (e.g. 8 points); c) estimate at best guess the presumed present state without sedation (e.g. 11 points), or d) regard the present assessment of consciousness as missing and thus deny a discount (i.e. 15 points). Although solution d) was emphasized by the authors of Apache II, all four will be found in the real world. The GCS is also part of the Multiple Organ Failure (MOF) score from Goris et al. [11], but as a result of a recent validation study in different centers it was decided to omit the GCS assessment because of its inaccuracy in intensive care patients.

Overestimation of accuracy

The ability of a score to correctly predict e.g. mortality, usually is expressed in terms of sensitivity (proportion of patients correctly predicted to die) and specificity (proportion of survivors correctly predicted to survive). These estimates are based on previous samples of ICU patients. But accuracy measures like sensitivity and specificity can strongly be influenced by the composition of the sample they are based on. If many patients with a low risk such as patients for short-term postoperative surveillance are contained in a sample of ICU patients, specificity might artificially be increased due to an "easy" prognosis of survival. In difficult clinical situations where clinicians need some additional information scores perform much worse than expected from their published accuracy. This is a further limitation of scores for use in the individual patient.

Conclusion

The scientific assessment and the practical use of score systems will undoubtedly continue or even increase. Scores can facilitate comparisons, enhance quality management, and improve clinical research. The usefulness of scores in the individual patient is limited due to the fact that scores reduce many dimensions of a clinical situation into a single value. Therefore, a score may supplement but will never replace clinical judgement, and those who use scores as a clinical routine should well know about the problems and limitation of scores.

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MEDIATORS AND PROSTAGLANDINS

Old and New Mediators in Sepsis
The Enigma Is Not Yet Resolved

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Sepsis may be defined as a systemic inflammatory response to an infection. The syndrome is characterized by alterations in temperature, leukocytosis, hypotension, hypoperfusion with cellular injury and organ failure often resulting in death.

The incidence of sepsis and sepsis related conditions has continued to increase during the last 30 years with a mortality rate of 35% [1].

Sepsis may be associated with infection by all classes of micro-organisms including Gram positive and Gram negative bacteria, fungi, parasites, protozoa and viruses.

These agents induce the synthesis and release of endogenous inflammatory and immunomodulating cytokines, which are essential to modulate the host response to infections.

Release of cytokines

TNF alpha and Interleukin beta (IL-1 beta) are known to exert an important pro-inflammatory action, activating neutrophils [2] and coagulation [3], stimulating neutrophil adhesion to the endothelium [4] and inducing apoptosis [5].

After endotoxin challenge TNF is the first cytokine to appear [6], peaking 90 minutes after endotoxin injection with transient release that varies in a wide range of concentrations (from few to thousands of pg/ml). Following the release of TNF, the circulating concentrations of other cytokines as IL-6, IL-8 macrophages inflammatory protein (MIP-1 alpha), monocyte chemoattractant protein-1 (MCP-1) increase as well [7, 8].

TNF is then responsible for the release of these secondary cytokines. Neutralisation of TNF activity in experimental endotoxemia prevented the release of IL-6 and IL-8 [9].

Blocking IL-6 activity does not affect the induction of other cytokines, indicating that IL-6 and IL-8 are more distal agents in the inflammatory cascade [10].

TNF and IL-6 were also shown to be implicated in the local inflammatory reaction in course of septic and non septic ARDS [11].

IL-8 can be produced from several types of cells, specifically: endothelial cells, macrophages, and polymorphonuclear leukocytes. It induces chemotaxis and activation of neutrophils.

The primary stimulus for this circulating IL-8 is not fully understood, but IL-1 and TNF are important inducers of IL-8 expression in many cell types [12].

IL-6 is a cytokine that can be produced by macrophages, lymphocytes, endothelial cells, and other tissues; it plays an essential role during the acute phase of the inflammatory response, acting synergistically with other compounds [13]. This peptide has been shown to be predictive for outcome in septic patients [13, 14].

Other cytokines such as IL-10 and granulocyte colony stimulating factor (G-CSF) are also released after sepsis or endotoxin administration [15, 16].

In animal models of sepsis G-CSF pre-treatment reduces endotoxin induced mortality and organ failure [17].

In humans G-CSF has been found to be beneficial in patients with pneumonia, burn injury and major trauma [18, 19].

The mechanism by which G-CSF regulates inflammatory reaction is not yet fully understood. In recent studies on human endotoxemia, G-CSF increased both pro- and anti-inflammatory responses [20].

In sepsis and experimental endotoxemia, circulating levels of IL-10 are increased, especially in meningococcal septic shock [21].

IL-10 seems to play a protective role in endotoxemia, as neutralisation of endogenously produced IL-10 resulted in increased mortality in endotoxin challenged mice. In humans administration of IL-10 causes a suppression of TNF and IL-1 beta production, while the production of their receptor antagonists remained unaltered [22].

Leukocyte activation

The emergence of leukocytes from the vascular to the interstitial compartment necessitates that the leukocytes come in contact with the blood vessel wall. Initially the leukocyte must be displaced from the blood stream towards the periphery of the vessels, a process which is mediated by the radial dispersal forces within the blood vessels [23]. In vivo observations suggest that this process of margination requires the interaction between red blood cells and leukocytes [24]. Following their margination, leukocytes undergo a series of adhesive interactions that starts with a rolling movement along vessel endothelium and is followed by a firm adhesion and subsequently, migration through the vessel wall (Fig. 1).

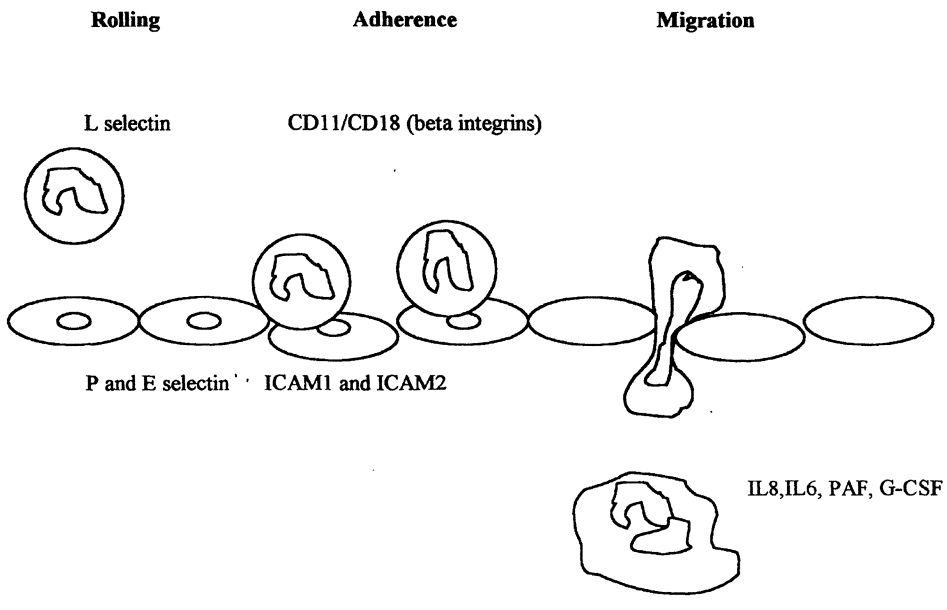

Fig. 1. After inflammatory stimulation the expression of selectins on endothelial cells increases, inducing an enhanced contact between endothelium and neutrophils. Leukocyte integrins promote the adherence of neutrophils onto the endothelial layer. Migration of neutrophils is induced by chemotactic agents as interleukins 8 and 6, platelet activating factor and granulocyte colony stimulating factor, etc

Leukocyte rolling in post-capillary venules may be enhanced by many substances and pathological conditions. Leukocytes rolling is mediated by a family of adhesion molecules located on both endothelial cells and leukocytes, known as selectin family of cell adhesion receptors. This family includes E and P selectin, which are expressed on the surface of stimulated endothelial cells. L selectins are expressed on the surface of all leukocytes [25]. The selectins are structurally similar carbohydrate-binding lecitins.

Firm adhesion between leukocytes and endothelial cells is mediated by the supergene immunoglobulins located on the surface of endothelial cells and their ligands, beta 2 integrins (CD11/CD18), which are expressed on most leukocytes [26]. Intracellular adhesion molecule 1 (ICAM1) has been implicated as a key modulator of leukocyte recruitment in several inflammatory models. The two alpha subunits of CD11/CD18, CD11a and CD11b, have been proposed as ligands for ICAM1. After intravenous endotoxin administration and following the stimulation by TNF, or chemotactic factors such as IL-8, G-CSF and platelet activating factor (PAF), CD11b/CD18 expression and activation on neutrophils increases [27].

Activation of the coagulation

A severe complication of sepsis is disseminated intravascular coagulation (DIC), which results from a deranged activation of the coagulation system with enhanced activation of coagulation, depression of the inhibitory mechanisms of coagulation, and inhibition of the fibrinolytic system.

Moreover, the consumption of clotting factors and platelets, due to the continuous activation of the coagulation system, may lead to severe bleeding disorders. The coagulopathy observed in sepsis have been well defined in studies of endotoxin and TNF-infused volunteers.

The common pathway of the coagulation system can be activated through the intrinsic and extrinsic way.

The intrinsic route is considered to result in the production of inflammatory mediators as bradykinin, which may be involved in the onset of hypotension during bacteremia [28].

The activation of the intrinsic pathway is well demonstrated in a considerable number of septic patients, however in human experimental endotoxemia results appear contradictory.

Animal studies of experimental endotoxemia have shown that TNF is a main mediator of endotoxin induced activation of fibrinolysis and IL-6 is relevant for the induction of the procoagulant response during endotoxemia [29].

Derangement of platelet count and activity represents another hallmark of septic condition. Hypopiastrinemia is in fact common during sepsis.

Furthermore, a recent clinical study have demonstrated that in septic patients platelets become activated and are hyperadhesive to other vascular cells including neutrophils and endothelial cells. This seems to induce sequestration of platelets and microcirculatory arrest, thus the development of multiple organ failure [30].

Apoptosis

Apoptosis is a form of cellular death, effected through the expression of an endogenous, genetically-regulated program, that results in the rapid elimination of the cell without evoking a significant inflammatory response. First recognised more than a century ago, this phenomenon is now believed to be central to the normal development of multi-cellular organisms, mediating such phenomena as tissue remodelling during embriogenesis, the deletion of autoreactive T cell clones during immune maturation, and the elimination of transformed cells by natural killer cells. It is also the mechanism through which cells with a fixed life span, such as epithelial cells and neutrophils die.

Early features of apoptosis include cytoplasmic blebbing, loss of normal cell-cell adhesion and elimination of specialized structures such as microvilli

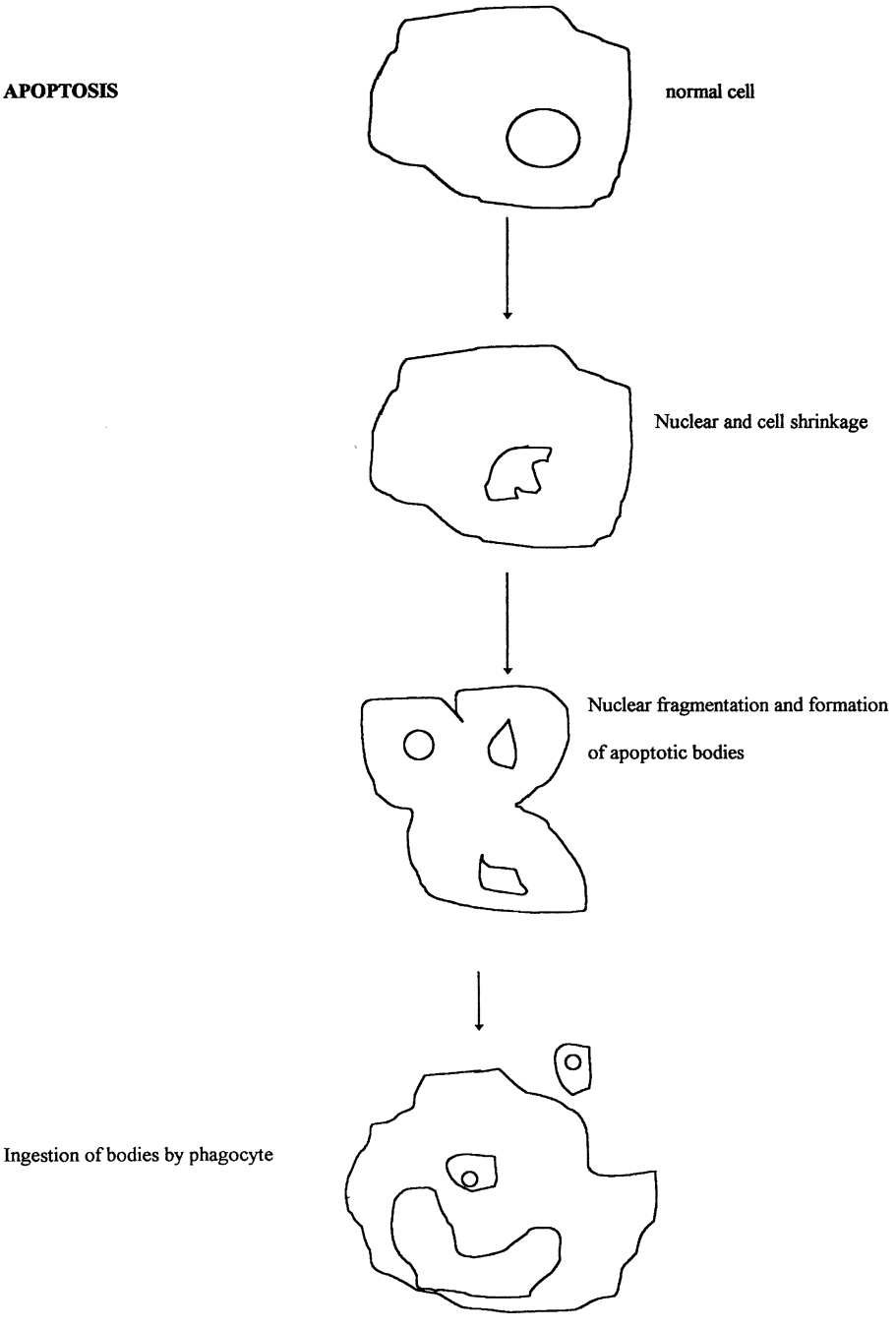

Fig. 2. Cell dying of apoptosis condenses and is phagocytosed by local macrophages, without inducing inflammation. The absence of a local response and the rapid evolution render the process less evident hystologically

(Fig. 2). In contrast to the cell dying a necrotic death, the apoptotic cell shrinks, its chromatin condenses and the nucleus fragments as a result of internucleosomal cleavage of DNA. Apoptosis occurs rapidly, and once triggered it is complete in 45 minutes.

Signalling pathways for apoptosis are incompletely defined. Generation of a ceramide from membrane sphingomyelin constitutes a key second messenger system leading to apoptosis [31]. Ceramide has also been reported to activate MAP kinase (MAPK) [32], and to mediate Fas- and TNF-induced apoptosis through activation of SAP kinase (SAPK).

Although apoptosis in critically ill patients has not been extensively studied, the available data show interesting abnormalities.

Lymphopenia is in fact common concomitant with trauma in critical illness. Studies in patients with major thermal injury show increased rates of apoptosis in peripheral blood lymphocytes [33].

Granulocyte macrophage-colony stimulating factor (GM-CSF) seems to modulate cell survival in systemic circulation [34].

An evolving understanding of the role of inflammatory cell apoptosis in the expression and termination of the host response to acute life threatening stimuli should provide the intensive care knowledge with new weapons to modulate the inflammation of the critically ill patient.

Conclusion

Due to the continuous improvement of knowledge on molecular and biological mechanisms of sepsis and sepsis related problems (only partially exposed in the present review), all researchers and clinicians fell victim of the illusion to be able of modulating the therapeutic approach.

Indeed, our present understanding of sepsis and organ failure needs to be revised, as the negative results of new therapies for these disorders suggest. Previous theories for the pathogenesis of these situations are incomplete for different reasons:

1. The models used to study these alterations are not analogous to the clinical situation.
2. Patients with less severe manifestations are often overlooked.
3. Patient's pre-existing conditions are not enough taken into account.

A considerable body of evidence indicates that together an important proinflammatory reaction, an anti-inflammatory response contributes to the onset of sepsis and organ failure.

At a local site of injury or infection and during the initial appearance of pro- and anti-inflammatory mediators in the circulation, the beneficial effects of these compounds counterbalance their harmful effects. Only when the balance

between these two forces is lost these substances may become harmful. The sequelae of an unbalanced systemic inflammatory reaction include derangement of microcirculation, shock, transudation into organs and defects of coagulation. An unbalanced systemic compensatory anti-inflammatory response often results in anergy and immunosuppression. The proinflammatory and anti-inflammatory conditions may ultimately reinforce each other, creating a state of destructive immunologic dissonance [35]. At the present time all the therapies that imply the block of a mediator or an inflammatory cascade should be carefully revised, as our present knowledge does not offer an adequate guarantee for their application in clinical practice.

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Modulating Prostaglandin Metabolism in

M.R. PINSKY

Sepsis is associated with a cacophony of activation and inhibit aspects of the host's inflammatory pathways. Because sepsis is by pro-inflammatory stimuli such as pancreatitis, trauma, end ous studies have focused on anti-inflammatory therapies in the patients with sepsis and septic shock. The mechanisms by whic processes induce inflammation and their regulation are central

Endotoxin infusion in the dog produces a generalized toxem is characterized by a shock state associated with diffuse org lactemia, and altered circulating levels of formed blood elemer morphonuclear leukocytes (PMN) and thrombocytes [1]. We shown that the associated generalized peripheral vascular paral tation-induced hyperdynamic state appear to reflect a loss of sy tone [22] occurring too early to be due entirely to nitric oxide (I inducible nitric oxide synthase [34]. Endotoxin induces these namic effects through a complicated process that includes the lease of inflammatory substances of the cyclooxygenase or lipo ways [2]. Although prior activation of pro-inflammatory medi in a more proximal position in the inflammatory cascade appea ble for the initiation of the inflammatory response [3] inhibitio nase and lipooxygenase pathways can prevent many of the hem of endotoxin administration in sheep [3, 4]. Presumably these occur despite an initial endotoxin-induced activation of both p cytokines and white blood cells [5]. However, the mechanism cyclooxygenase or lipooxygenase inhibition alters the inflamm endotoxin is unclear. We have previously shown that pretreatm fen, a reversible cyclooxygenase inhibitor, though abolishing th endotoxemia on blood pressure and cardiac output, does not pr ated increasing in O_2 consumption or lactic acidosis [21] processes in the expression of the endotoxic state may be contro ferent mediators.

The systemic manifestations of endotoxemia are essentially host in response to endotoxin through the synthesis and release sis factor-α (TNF-α) [6]. TNF-α both stimulates further cytoki

has direct cytotoxic effects in vitro [7]. Furthermore, TNF-α infusion can mimic many of the hemodynamic effects of acute endotoxemia in the dog [8]. After TNF-α release, further stimulation of the monocyte pool results in the synthesis and release of numerous other cytokines that have diverse regulatory functions within the inflammatory process [9]. Interleukin-6 (IL-6) appears to be central in the global metabolic response to sepsis in man [10]. However, IL-6 by itself does not appear to induce any significant hemodynamic alteration [11]. We previously assayed a large battery of cytokines over time, including TNF-α, IL-1, IL-2, IL-6, and interferon-γ from the blood of humans with sepsis and found that only TNF-α and IL-6 are consistently elevated at any time in those subjects. Furthermore, if elevate TNF-α and IL-6 levels are sustained, they are highly predictive of the subsequent development of multiple system organ failure and death [12]. Subsequently, we demonstrated that variations in systemic IL-6 levels parallel variations in PMN up-regulation of the potent cell adhesion molecule CD-11b [13] in critically ill humans. These data suggest that sustained serum cytokine elevations induce activation of circulating immune effector cells inducing end-organ dysfunction and death in man.

Exactly how cytokines release induces subsequent cardiovascular changes and organ injury is not only a complex process but poorly understood. It is known, however that ecosinoid metabolism is intimately related to this process through the elaboration of both prostanoid (PG), leukotriene (LT) and platelet activating factor (PAF) metabolism. Ecosinoids, such as LTB4, LTD4, thromboxane A_2, $PGF_{2\alpha}$ and PGE_1 are all released into tissue compartments and their metabolic breakdown products are measurable both in these compartments and in the blood of both septic patients and experimental sepsis animals. These ecosinoid metabolites induce PMN adhesion and migration, increased capillary permeability.

Potentially, inhibition of ecosinoid metabolism may blunt the initial systemic inflammatory response minimizing subsequent organ injury and secondary cytokine up-regulation. However, the pattern of cytokine response to acute endotoxin infusion in the dog is unclear and the effect of pretreatment with either a cyclooxygenase or lipooxygenase inhibitor has not been described.

Northover and Subramanian [14] first demonstrated that non-steroidal anti-inflammatory drugs ameliorate the cardiovascular effects of endotoxin in the canine model, presumably by inhibiting cyclooxygenase. We subsequently demonstrated that pretreatment with ibuprofen, a competitive cyclooxygenase inhibitor blocked the hemodynamic but not metabolic consequences of acute endotoxemia in an acute canine model [21]. Ibuprofen pretreatment may beneficially affect long-term outcome after endotoxin exposure either by preventing the initial endothelial injury induced by the endotoxin-stimulated release of cytokine [15] or by altering the subsequent response of formed cellular elements [16] as prostaglandins inhibit human monocyte production of cytokines [17]. According to the above hypothesized mechanism, we would predict that although the initial serum cytokine levels in response to endotoxin infusion would be unaffected or

possibly increased by ibuprofen pretreatment, subsequent cytokine levels would decrease rapidly toward baseline values and be associated with normalization of hematological and metabolic markers of system stress. Because TNF-α has a serum half-life of less than 20 minutes [6], serum TNF-α levels measured at a later time should be reduced toward pre-insult levels in animals pretreated with ibuprofen. Furthermore, associated markers of a systemic inflammatory response, such as circulating polymorphonuclear leukocytes and thrombocytes, oxygen supply-demand ratios, and arterial blood lactate levels, should parallel serum cytokine kinetics.

Although cyclooxygenase inhibition with ibuprofen has been extensively studied in models of endotoxic shock, leukotriene D_4 synthetase inhibition with diethylcarbamazine (DEC) has not. Recent studies in murine models of endotoxic shock suggest that lipooxygenase inhibition can modify the inflammatory response to endotoxin [18]. Furthermore, this modulation appears to be dependent on baseline hepatocytic function [19]. Because IL-6 appears to function primarily as a metabolic cytokine, and because the liver is one of its primary targets, we further wished to define the effect of DEC pretreatment on TNF-α and IL-6 kinetics in a dog model of endotoxic shock.

Potentially, prior cyclooxygenase or 5-lipooxygenase inhibition should not alter the initial cytokine or WBC response to a septic challenge, but would limit the duration of any systemic cytokine elevation in response to that challenge by limiting feed back activation of the initial pathways of inflammation. To examine these interactions, we pretreated dogs with either ibuprofen, a cyclooxygenase inhibitor, or DEC, a 5-lipooxygenase inhibitor prior to inducing endotoxic shock with a bolus infusion of E. coli endotoxin.

In control animals, not surprisingly, endotoxin infusion resulted in an immediate decrease in blood pressure, cardiac output, and white blood cell count (WBC) and platelet levels and an increase in heart rate (HR). Serum TNF-α and IL-6 levels increased following both the minor surgical manipulation and endotoxin infusion. The levels of both cytokines decreased progressively over the next three hours. The response to endotoxin infusion in the ibuprofen group was different from that in the control group. Interestingly, blood pressure and serum lactate levels unchanged, while cardiac output, WBC and platelet levels all decreased to levels similar to control animals. Furthermore, the increase in serum TNF-α and IL-6 levels after endotoxin infusion were similar to that in control dogs after endotoxin infusion, although the IL-6 levels started at a higher initial value in the ibuprofen group. Presumably, ibuprofen increased IL-6 levels independent of endotoxin. Unlike ibuprofen pretreatment, DEC infusion induced a transient decrease in blood pressure and an increase in both cardiac output and IL-6 levels, consistent when a selective drug-induced vasodilatation plus a nonspecific activation of IL-6 release. However, DEC pretreatment had no other measurable effect on hemodynamic profile data before endotoxin infusion. Interestingly, serum IL-6 levels were the highest following endotoxin challenge in this group when compared with the two others. Interestingly, when we fluid

challenged these dogs and calculated a $\dot{V}O_2/DO_2$ relation, we saw that prior to endotoxin challenge $\dot{V}O_2$ remained constant, whereas following endotoxin challenge, the $\dot{V}O_2/DO_2$ relation was linear such that they co-varied. Blocking the arachidonic acid pathways did not alter this change. These data suggest that arachidonic acid metabolites play a more complex role in the regulation and expression of acute endotoxemia than just as amplifiers of the inflammatory signal.

Infusion of endotoxin results in a rapid decrease in arterial pressure and cardiac output, and a progressive increase in blood lactate levels [1]. Furthermore, Pinsky and Matuschak [22] demonstrated that the immediate decrease in arterial pressure and cardiac output was due to a reduction in venous return, presumably due to venous pooling, whereas in the fluid-resuscitated dog, the changes in steady-state arterial pressure and cardiac output could be explained by a decrease in arterial closing pressure with a minimal change in incremental resistance. Pinsky [21] subsequently demonstrated that ibuprofen pretreatment abolished the observed decreases in both arterial pressure and blood flow occurring after a bolus infusion of endotoxin but did not prevent the endotoxin-induced increase in $\dot{V}O_2$. Changes in DO_2 do not normally alter $\dot{V}O_2$ in a resting animal whose DO_2 exceeds 10 to 12 $ml/kg^{-1}/min^{-1}$ of oxygen [20]. Our data on the $\dot{V}O_2/DO_2$ relation before infusion of endotoxin support these findings. However, post-endotoxin levels of blood lactate were increased, while $\dot{V}O_2$ and DO_2 co-varied. These data agree with those from our previous study on patients in septic shock, in which changes in DO_2 proportionally altered $\dot{V}O_2$ only when blood lactate levels were high [23]. Interestingly, post-endotoxin levels of $\dot{V}O_2$ never exceeded pre-endotoxin levels, even at maximal intravascular volume levels during the fluid challenge runs, despite similar DO_2 levels after volume infusion. These data suggest that the covariance of $\dot{V}O_2$ and DO_2 in our model may reflect impaired oxygen extraction in the tissues. Previous research has shown that endotoxin infusion induces a transient reduction in WBC and platelet levels because of the margination of these formed blood elements in the periphery [24]. Our data agree with those of others and serve as baseline data to compare the effects of ibuprofen and DEC.

Products of both cyclooxygenase and lipooxygenase metabolism appear to be central to the hemodynamic response to endotoxin because a) their levels are increased in the blood and tissues after endotoxemia [4, 9, 19, 25], b) they can cause many of the observed hemodynamic, cellular, and metabolic effects seen during endotoxemia, if given alone [9, 26]; c) in disease states where clearance of these inflammatory mediators is impaired, survival from septicemia is dramatically reduced [18, 25], and d) specific inhibitors of both metabolic pathways improve survival in animals given endotoxin [24, 27]. As previously reported [28, 30], ibuprofen increased pulmonary vascular resistance. The cause of this increase may be the inhibition of synthesis of vasodilatory escosinoids, such as PgE_1 and PgI_2. Numerous investigators have studied the effects of cyclooxygenase and 5-lipooxygenase inhibition and/or LTD_4 antagonists on endotoxin-induced changes in pulmonary and systemic hemodynamics [4]. These

studies demonstrated that neither cyclooxygenase inhibitors nor LTD_4-antagonists prevent endotoxin-induced changes in WBC count despite the observed marked protective effects of these therapies on pulmonary and systemic hemodynamics. Interestingly, a calcium channel blocker, verapamil, is one of the few agents shown to prevent both endotoxin-induced changes in hemodynamics and WBC changes [29]. Although these studies were done in a different animal species (sheep), both the time course and magnitude of the hemodynamic responses were similar.

Importantly, our preliminary study supports the previous findings of others [30], who reported that pretreatment with ibuprofen can block many of the observed acute hemodynamic effects of bolus endotoxin infusion in the dog. However, ibuprofen pretreatment does not appear to alter either the blood component or cytokine response to endotoxin infusion over an initial 3 hour interval. Furthermore, others have shown that ibuprofen pretreatment in humans may augment the TNF-α and IL-6 response to low-dose endotoxin infusion [5, 31]. Accordingly, ibuprofen appears to mask the effects rather than inhibit the activation of proximal inflammatory mediators and their effects on formed blood elements. Thus, the observed beneficial effects of ibuprofen pretreatment in the management of animals with endotoxic shock appears to be due to actions that are indirectly related to the short-term release of inflammatory mediators into the blood. Furthermore, in patients with documented septic shock [12], TNF-α levels decrease considerably within the first 4 hours without treatment with cyclooxygenase inhibitors.

As previously described, DEC induced a transient hypotensive response characterized by tachycardia, decreased arterial pressure, and increased cardiac output, suggesting that selective loss of arterial vasomotor tone induces this effect [19]. Furthermore, we found that serum IL-6 levels were markedly increased after administration of DEC. DEC did not abolish the hemodynamic response to endotoxin, but rather exaggerated it by a sustained tachycardia. DEC may reduce arterial resistance, thereby increasing peripheral blood flow. In support of this hypothesis, blood lactate levels, although increased after exposure to endotoxin, returned to pre-endotoxin levels by 3 hours. DEC does not appear to affect the TNF-α response to endotoxin. Serum IL-6 levels tended to be higher after endotoxin, but these differences were insignificant.

Interestingly, we saw significant increases in serum TNF-α and especially IL-6 levels in those dogs pretreated with DEC. To our knowledge, no one has ever demonstrated an enhanced inflammatory response to endotoxin with lipooxygenase inhibition. Furthermore, DEC has been shown to reduce, not augment, the inflammatory response to endotoxin in the rat with acute liver failure [19]. There are three explanations for the DEC findings. First, products of lipooxygenase metabolism may function to minimize the host response to endotoxin. However, this explanation seems unlikely because normal lipooxygenase pathway end-products are inflammatory in nature, whereas cyclooxygenase pathway end-products have both inflammatory and anti-inflammatory properties

[9]. Second, DEC may incompletely inhibit all lipooxygenase activity [32]. DEC is a competitive inhibitor of lipooxygenase. Its pharmacological actions may allow partial lipooxygenase activity to continue or shunting of arachidonic acid metabolism toward increased production of platelet activating factor to occur. Although interesting to speculate upon, this explanation can be neither refuted nor proved. Third, DEC may also induce tissue injury, such that its effects become synergistic with those of endotoxin. We usually observed some degree of hypotension after DEC infusion in all animals. This hypotensive response could be minimized by decreasing the DEC infusion rate.

No animal model accurately represents human sepsis. However, numerous investigators have attempted to explore the pathophysiologic processes operative in sepsis by examining the effects of endotoxin infusion on the canine cardiovasculature [1, 22, 24, 27, 28]. Although the cardiovascular response to endotoxin appears to be both time- [1, 22] and dose-dependent [19], most studies have shown that endotoxin produces an immediate decrease in arterial pressure and cardiac output that is associated with a progressive increase in serum lactate levels, with subsequent cardiovascular effects being dependent on the method of administration and amount of endotoxin infused [1, 19]. This hypotensive effect becomes more pronounced as the amount and rate of endotoxin infusion increases. Furthermore, the fall in cardiac output seen during endotoxemia is a function of circulating blood volume [22]. In our study, we performed an exchange transfusion to acquire autologous iso-hematocrit blood for the fluid challenge runs and were surprised to find that exchange transfusion increased serum levels of both TNF-α and IL-6 and that the rise in TNF-α levels of some animals were similar to those seen after endotoxin infusion. The cause of this effect is unclear. Since we used hydroxyethylstarch infusion as the oncotic balance of the blood removal, we may have altered blood monocyte function. However, in a study in rats, Schmand et al. [33] demonstrated the hydroxyethlystarch augmented IL-6 expression by macrophages. It is unclear if DEC and hydroxyethylstarch co-stimulated release of IL-6 in that animal sub-group but it can partially explain the increases in IL-6 seen in the blood following exchange transfusion in all animals. Furthermore, the immunocompetent cells in the reserved blood may also have been producing TNF-α and IL-6, which would then increase blood cytokine levels further during re-infusion. Subsequent studies in humans have failed to document measurable increases in TNF-α, IL-6 or IL-8 levels in shed blood over similar time interval [35]. Furthermore, it is doubtful that the stored blood was producing significant amounts of cytokines because serum TNF-α and IL-6 levels decreased during the fluid challenge run before endotoxin infusion; if mediators were also being infused with the blood, these levels should have increased.

Clinical studies, which have attempted to alter prostaglandin metabolism in sepsis, are few. Unfortunately, all have proven negative in their ability to improve outcome [36]. The initial studies of PgE_2 infusions in acute respiratory distress syndrome and the recent study of ibuprofen treatment for sepsis clearly

demonstrate that the non-specific use of these agents in sepsis is not recommended. Clearly, if these agents which either supplant or inhibit arachidonic acid metabolism are to be used clinically, they will need to be given within the framework of continual monitoring of a specific end effect, which at present has not been defined.

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$DO_2/\dot{V}O_2$ IN SEPSIS

Oxygen Delivery and Consumption Relationships in Sepsis - The Role of Inotropic and Vasoactive Drugs

O. BOYD

Introduction

Historical background

Oxygen delivery (DO_2) and oxygen consumption ($\dot{V}O_2$) relationships are a confusing subject with contradictory research findings. Whole body DO_2, also termed oxygen availability, is calculated: DO_2 = Hb x SaO_2 x CO x 0.134, where Hb = hemoglobin concentration, g/dl; SaO_2 = arterial oxygen saturation, %; CO = cardiac output, l/min. $\dot{V}O_2$ can either be calculated indirectly, Hb x (SaO_2 - SvO_2) x CO x 0.134, where SvO_2 = venous oxygen saturation, or be directly measured as the difference between inspired and expired gases. In normal individuals $\dot{V}O_2$ is closely regulated to provide for the bodies needs and remains relatively constant over a wide range of DO_2. If DO_2 falls however, a critical point is reached after which $\dot{V}O_2$ also falls. A different situation might occur in critically ill patients, particularly septic patients, where $\dot{V}O_2$ appears to be related to DO_2 over a wide range of DO_2, a phenomenon termed "supply dependence" [1].

The "supply dependence" of $\dot{V}O_2$ on DO_2 allows possible rational therapy - DO_2 is increased by inotropes to increase $\dot{V}O_2$, to prevent an oxygen debt and hypoxic damage. It was suggested that an "oxygen flux test" should be conducted in all critically ill patients and two early clinical trials also tended to show improved outcome in septic patients [2, 3].

Problems and questions

The biggest problem is that no studies have convincingly demonstrated that manipulating DO_2 and $\dot{V}O_2$ in septic patients has a positive effect on outcome (this is quite a different situation to the peri-operative patient) [4]. This paper considers the problems inherent in the interpretation of DO_2 and $\dot{V}O_2$ data and then looks at the role of vasoactive medication in human sepsis and septic shock.

The interpretation of DO_2 and $\dot{V}O_2$ data

Experimental methodology

The methods that have been used to investigate the relationship between DO_2 and $\dot{V}O_2$ may be flawed. Many early studies induced changes in DO_2, e.g. by addition of PEEP, and subsequently showed changes in $\dot{V}O_2$. However, DO_2 changes were over a narrow range, and changes in $\dot{V}O_2$ over wider ranges cannot be implied. Moreover, showing reduction in both parameters may not allow the conclusion that both will increase together.

Data analysis

Pooled data is often used for analysis, this may show correlation between the parameters for the population, whereas there may be no correlations for the parameters for any individual. A further mathematical consideration is the use of a shared measurement variable, cardiac output, in the calculation of both DO_2 and $\dot{V}O_2$ [5]. However, in the clinical situation the importance of mathematical coupling may have been over emphasised as a number of trials which have manipulated DO_2 and measured $\dot{V}O_2$ indirectly have not shown any correlation between DO_2 and $\dot{V}O_2$ [6].

Changes in oxygen demand

Many interventions can effect oxygen demand. The normal physiological response to an increase in demand is to increase oxygen supply, giving an identical positive relationship between DO_2 and $\dot{V}O_2$ as in the "supply dependent" situation. However, the relationship here will be *demand* led, not supply led. For example, temperature causes an increased $\dot{V}O_2$ [7]. Changes in sedation and paralysis also change oxygen demand. We demonstrated that variations in DO_2 and $\dot{V}O_2$ that occurred during variations in sedation level in critically ill postoperative patients mimicked "supply dependence" [8]. Moreover, there are wide swings in metabolic rate in ICU patients, occurring due to changes in arousal, the resultant variations in oxygen transport can mimic supply dependence [9].

A further complication is the fact that increasing blood flow to some organ systems will increase their metabolic demand. The heart is an obvious example, increased blood flow requires increased work and increased myocardial $\dot{V}O_2$. In the kidney, increased renal blood flow and glomerular filtration requires increased metabolic work and $\dot{V}O_2$ for active solute absorption. In these situations a "supply dependent" relationship between DO_2 and $\dot{V}O_2$ actually exists, but is not due to a previously unmet demand for oxygen. On the contrary, an increase in supply is driving the need for increase in $\dot{V}O_2$.

The thermogenic effect of drugs

It has been known for many years that catecholamines are potent stimuli for increasing metabolic rate in humans [10], due to increases in cellular metabolic rate and flow changes. Many of the interventions used to increase DO_2 in critically ill patients involve the use of catecholamines, and dobutamine has been advocated as an agent to be used as part of the "oxygen flux test" in the critically ill. However, epinephrine, norepinephrine, dopamine, dobutamine, and combinations of agents have all been shown to increase $\dot{V}O_2$ in normal volunteers. If both flow and $\dot{V}O_2$ are increased by the addition of a catecholamine in normals, the conclusion that when both occur in the critically ill there is evidence of oxygen debt does not seem logical.

More recently two studies have re-evaluated the prognostic value of the relationship between DO_2 and $\dot{V}O_2$. Bihari et al. showed that a positive relationship between DO_2 and $\dot{V}O_2$ indicated a poor prognosis [11]. In contrast, Vallet et al. showed that if $\dot{V}O_2$ is increased by a short-term infusion of dobutamine in septic patients the prognosis for the patients is much better [12]. They suggest that in patients who show an increase in $\dot{V}O_2$, cellular metabolism is responding as normal, but a failure of response indicates a cellular metabolic defect. Although not all studies show a survival difference between responders and non-responders [13], Vallet's paper is potentially of major importance as it questions the whole rational for increasing DO_2 and $\dot{V}O_2$ as a therapeutic tool.

The influence of inotropes and vasodilators on DO_2 and $\dot{V}O_2$

Despite the large number of studies in this area, in both patients and animal models, no consensus of opinion has emerged, and apparently similar studies often give conflicting results. The reasons for this may be detailed above, but even when there is some agreement the clinical relevance is not known. There is also doubt as to the bioavailability of the agents used. Moreover, it is by no means certain that the variations in $\dot{V}O_2$ are of importance in themselves. In some studies $\dot{V}O_2$ has remained unchanged while supposed markers of organ perfusion, such as gastric intramucosal pH (pHi), have improved.

Dobutamine

Dobutamine is the most widely studied agent, and has been traditionally shown to increase both DO_2 and $\dot{V}O_2$ in patients with sepsis and septic shock [14], particularly if lactate was high. However, the therapeutic importance of this is in doubt. In the early trials Edwards et al. [2] showed improved outcome in patients with septic shock but only compared to historical controls. Tuchschmidt et al. [3], demonstrated improved survival in the group treated with "goal-directed" therapy, but this did not reach statistical significance. More recently larger

studies have also failed to show improvement in outcome in critically ill patients, many of whom were septic, when the investigators tried to attain the goals for cardiac index and DO_2 [6, 15]. Furthermore, in Hayes' study [6] there were no changes in $\dot{V}O_2$ in the group treated to attain the higher DO_2.

Other recent studies have also shown that the effect of dobutamine may be variable. In patients with sepsis and ARDS, dobutamine increased DO_2 and $\dot{V}O_2$ in only 8 of 12 patients, and this had no relationship to lactate levels [16]. In another study patients with severe sepsis showed no increase in $\dot{V}O_2$, whether or not they had a high lactate, and regardless of whether dobutamine or military antishock trousers were used to increase DO_2 [17]. However, in other studies the relationship between rise in DO_2 and rise in $\dot{V}O_2$ continues to be found [13].

Other vasoactive agents

Dopexamine has been recommended to increase splanchnic and renal blood flow and oxygenation [18], but there is little published work on $DO_2/\dot{V}O_2$ changes. Smithies et al. showed a rise in pHi and improvement in liver function accompanying an increase in DO_2 in 10 septic patients [19]. In another study of 29 septic patients dopexamine led to an increase in DO_2 and a 4-8% increase in $\dot{V}O_2$ [20]. In this study oxygen extraction ratio fell and the authors suggested that the rise in $\dot{V}O_2$ might be due to calorigenic effects and increased myocardial $\dot{V}O_2$.

Norepinephrine is widely used for the maintenance of blood pressure in septic shock, but once again its effects on DO_2 and $\dot{V}O_2$ have been less well documented. Schreuder et al. reported that norepinephrine increased $\dot{V}O_2$ but not DO_2 in patients with septic shock, presumably due to rise in perfusion secondary to rise in mean arterial blood pressure [21]. However, in a study of 28 patients with septic shock, 15 received norepinephrine, and while there were no changes in global DO_2 or $\dot{V}O_2$, but there were significant rises in splanchnic DO_2 and $\dot{V}O_2$ without change in pHi [22]. In contrast, a study comparing dopamine and norepinephrine in septic shock patients showed increases of DO_2 and $\dot{V}O_2$ with both agents but an increase in pHi only with norepinephrine, this despite a higher cardiac output with dopamine [23]. If dopamine is substituted for dobutamine or norepinephrine in stable patients with septic shock, there is no further increase in $\dot{V}O_2$ despite increases in DO_2 [24].

Bollaert et al. investigated the use of epinephrine in 13 patients with septic shock, and showed that both DO_2 and $\dot{V}O_2$ could be elevated [25]. Other vasopressor medication has also been used in septic shock. In a cross-over study of 12 patients with septic shock a nitric oxide synthetase inhibitor was administered, although mean arterial pressure rose there was a fall in cardiac output and DO_2 [26]. However, in a trial of methylene blue in patients with septic shock, short term infusion resulted in increase in MAP, without detrimental changes in cardiac output, DO_2 or $\dot{V}O_2$ [27], and another study has even shown rise in DO_2 and $\dot{V}O_2$ [28].

Conclusion

Although in the 1980's it appeared that understanding of the relationship between DO_2 and $\dot{V}O_2$ in septic patients might herald the onset of new and successful therapeutic options, the early promise has not been fulfilled. No clear picture of the effect of inotropes or vasoactive medication on DO_2 and $\dot{V}O_2$ in human sepsis has emerged, and no trials have demonstrated that manipulation of these parameters has any effect on mortality.

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COAGULATION

Disturbances and Modulators of Coagulation and Fibrinolysis in Sepsis

L.G. THIJS

In patients with sepsis abnormalities in hemostatic variables indicating systemic activation of coagulation and early activation with subsequent inhibition of fibrinolysis, are common features [1-5]. The most important clinical manifestation of these processes is disseminated intravascular coagulation (DIC), which is characterized by generation and deposition of fibrin in the microvasculature with widespread microvascular thrombosis in various organ systems. The biphasic effect on the fibrinolytic system may result in impaired fibrin dissolution and aggravate the formation of microthrombi. There is evidence that DIC contributes to the development of (multiple) organ dysfunction and failure [3, 5]. In addition, depletion of coagulation proteins and platelets, mainly due to the extensive and ongoing coagulation activation, may induce severe bleeding complications [6]. The impressive extreme of the clinical spectrum of manifestations of DIC is purpura fulminans, which presents with hemorrhagic skin necrosis and peripheral gangrene and is most often seen in meningococcal sepsis [7].

Sepsis appears to be the most common cause of acute DIC and DIC is a relatively frequent complication of sepsis with major implications for morbidity and mortality. Septic patients who develop DIC have a higher mortality rate and have more organ dysfunction than patients who do not have signs of DIC [3]. The reported prevalence of DIC in large clinical trials in septic patients varies between 7.5 and 49%, depending on the type of patients and the definition used for DIC [8-13]. Generally the prevalence is higher in the more severe forms of sepsis, e.g. septic shock, than in the milder forms. In a large prospective study the incidence of DIC in patients with sepsis was 16%, in severe sepsis 18% and in septic shock 33% [14].

Coagulation and fibrinolysis

In the classical concept of coagulation thrombin is generated by either the extrinsic (tissue factor-dependent) pathway or the intrinsic (contact activation-dependent) pathway of coagulation. Although both pathways can be activated in sepsis, recent studies using highly specific and sensitive assays for activation

products of coagulation indicate that activation of coagulation in sepsis is primarily driven by the tissue factor-dependent pathway. In non-human primates challenged with endotoxin, the blocking of the extrinsic pathway by simultaneous infusion of monoclonal antibodies directed against tissue factor or factor VII almost completely inhibits thrombin generation and fibrinogen-to-fibrin conversion [15, 16]. Conversely, the blocking of the intrinsic pathway in septic baboons with infusion of a monoclonal antibody against factor XII did not prevent coagulation activation [17]. Therefore, the concept of coagulation has changed and the extrinsic and intrinsic pathway have essentially merged into one series of interrelated reactions that are initiated by expression of tissue factor [18]. During sepsis tissue factor can be expressed on monocytes and endothelial cells. Monocytes generate after exposure to endotoxin measurable quantities of mRNA encoding the tissue factor molecule which is then rapidly synthesized and surface exposed [19]. Monocytes isolated from blood of patients with meningococcal sepsis show increased tissue factor expression and highest expression was associated with a high mortality rate [20]. Endotoxin can also in vitro enhance tissue factor expression on endothelial cells, a process that is slower than in monocytes and takes a few hours [21, 22].

Cell surface-expressed tissue factor binds and activates factor VII, thereby forming the factor VIIa-tissue factor complex which activates factor X and factor IX. Factor Xa together with factor Va converts prothrombin to thrombin (and fragment F1 + 2). Factor IXa together with factor VIIIa can activate additional factor X. Thrombin can catalyze the conversion of factor XI to factor XIa which activates factor IX. Thrombin cleaves fibrinogen, yielding monomeric fibrin which then polymerizes to form the fibrin clot [23].

Coagulation is regulated by natural inhibitors of coagulation: the antithrombin III (ATIII)-heparin sulfate system, the protein C (PC)-protein S (PS) system and tissue factor pathway inhibitor (TFPI). ATIII binds to and inactivates thrombin generated during the clotting process and forms the thrombin-antithrombin (TAT) complex and also inactivates other activated coagulation factors [23]. TAT complexes are sensitive markers of in vivo thrombin generation [24]. This complex formation is accelerated by exogenous heparin but also by endogenous heparin sulfates produced by endothelial cells. Synthesis of these glycosaminoglycans is inhibited by endotoxin [25].

Protein C is activated by complexes of thrombin with the endothelial cell surface protein thrombomodulin. Activated PC is an important inhibitor of the coagulation cofactors Va and VIIIa and also enhances fibrinolysis by binding and inactivating plasminogen activator inhibitor-1 (PAI-1) [23]. In vitro, endotoxin can suppress thrombomodulin expression on endothelial cells [21]. Also, granulocyte proteases and oxygen radicals which are generated during sepsis can in vitro inactivate thrombomodulin [26]. Activated PC can be inhibited by a heparin-dependent protein C inhibitor and by α_1-antitrypsin [27]. Protein S serves as a cofactor for activated PC and exists in plasma in two forms: as free protein which is active and as an inactive form complexed with C4b-binding

protein (C4BP). C4BP may, therefore, serve as an inhibitor of PS activity. PS functions by enhancing the cell surface anticoagulant activity of activated PC. C4BP is an acute phase protein and its level may increase in sepsis and bind PS.

It therefore seems that in sepsis various mechanisms may impair activity of the PC-PS system and thereby promote coagulation.

TFPI produced by endothelial cells is a potent but slow inhibitor of the factor VIIa-tissue factor complex and can also inhibit factor Xa directly [28, 29]. The importance of these natural inhibitors has been demonstrated in a number of studies in non-human primates. High dose ATIII [30], activated PC [31] and recombinant TFPI [32, 33] reduce the coagulopathic and cell injury responses to an infusion of a lethal dose of live E. coli and prevent death. Conversely, blocking of PC activation with an anti-PC monoclonal antibody [31] or infusion of C4BP [34] in this model infused with a sublethal dose of E. coli increases organ injury and promotes mortality.

Fibrinolysis plays an important role in regulating the formation and the removal of microthrombi. The fibrinolytic system is an endogenous system which seems to preserve the microcirculation from irreversible damage. Fibrinolysis is initiated mainly by the release of tissue-type plasminogen activator (t-PA) released from endothelial cells. The role of another plasminogen activator urokinase plasminogen activator (u-PA) which can be released from various cell types has not been clearly defined [35]. t-PA converts the zymogen plasminogen into the active enzyme plasmin which enzymatically degrades fibrin into fibrin degradation products. Also activation of the contact system which is initiated by factor XII activation can activate fibrinolysis [36].

Fibrinolysis is attenuated at two levels. First, t-PA (and also u-PA) activity is inhibited by plasminogen activator inhibitor-1 (PAI-1) which binds to and inactivates t-PA. Endothelial cells are capable of releasing PAI-1 [37]. On the other hand activated PC enhances fibrinolysis by binding to and neutralizing PAI-1. Second, plasmin binds to its endogenous inhibitor α_2-antiplasmin to form plasmin-antiplasmin (PAP) complexes, whereby plasmin activity is neutralized. The presence of PAP complexes in plasma is a direct indication of in vivo plasmin generation. In vitro, cell cultures of human endothelial cells show no change or a decrease in t-PA release [38, 39], whereas the release of PAI-1 is increased [38, 40]. Endotoxin, therefore, seems to inhibit the fibrinolytic capacity of endothelial cells.

Early dynamics of coagulation and fibrinolysis in experimental septic models: role of cytokines

Studies in human volunteers and non-human primates challenged with a low dose endotoxin have clarified the early route and dynamics of activation of coagulation and fibrinolysis. In these models a rise in plasma concentration of pro-

thrombin fragment F1 + 2 and TAT complexes is observed, becoming evident from 2 hours after the challenge [15, 41-43]. Activation of coagulation is, however, preceded by a rapid and transient activation of fibrinolysis. Following endotoxin injection levels of t-PA rise rapidly starting at 1 hour postinjection and paralleled by a rise in PAP complexes, indicating in vivo plasmin generation [15, 41-45]. This is followed by an increase in PAI-1 levels starting at about 2 hours postinjection [15, 41-45]. Apparently, fibrinolysis is inhibited as evidenced by a fall of PAP levels after the rise in PAI-levels, whereas coagulation activation is still proceeding. Thus, several hours after endotoxin injection coagulation is ongoing and fibrinolysis is offset, creating a procoagulant state. Such a dysbalance of coagulation and fibrinolysis has also been observed in non-human primates following infusion of (sub)lethal doses of live E. coli [46].

During sepsis many endogenous mediator systems are activated [47]. These activated mediators are largely responsible for the clinical signs and symptoms of sepsis. Release of cytokines (TNFα, IL-1, IL-6, IL-8, etc.) from activated macrophages and endothelial cells is an early event after a bacterial challenge [48].

There is much evidence that the effects of endotoxin on coagulation and fibrinolysis are mediated by cytokines. First, TNF and IL-1 are able to enhance in vitro the expression of tissue factor in cultured human endothelial cells [49, 50] and monocytes [51]. Also, these cytokines can in vitro downregulate thrombomodulin activity in endothelial cells, thereby inhibiting their anticoagulant properties [52, 53]. TNF and IL-1 can also affect the fibrinolytic properties of endothelial cells, the overall effect being an impairment of fibrinolysis, mainly by stimulating the release of PAI-1 [38, 54]. Second, a bolus injection of recombinant TNFα in healthy individuals induces a sustained thrombin generation as evidenced by elevated levels of prothrombin fragment F1 + 2 [55]. This is preceded by early activation of fibrinolysis mediated by a rise in t-PA, followed by sustained inhibition due to a rise in PAI-1 levels [56]. Similar changes in coagulation and fibrinolysis have been observed in patients with malignancies infused with TNF for 24 hours [57, 58]. The TNF-induced signs of activation of coagulation and fibrinolysis are similar to those induced by endotoxin except that they occur about 1-2 hours earlier, suggesting that endotoxin acts via TNF release. Third, administration of endotoxin in combination with pentoxifylline, a compound that can inhibit release of TNF by macrophages and mononuclear cells in non-human primates inhibited endotoxin-induced activation of coagulation and strongly attenuated the fibrinolytic response [15, 45]. These observations suggest a central role for TNF as activator of coagulation and fibrinolysis. However, in the same experimental model an anti-TNF monoclonal antibody did not influence endotoxin-induced activation of coagulation as reflected by unchanged increases in levels of prothrombin fragment F1 + 2 and TAT complexes [42]. Whereas coagulation was not inhibited, fibrinolysis was completely suppressed [42, 45]. In addition, administration of recombinant IL-1α in the experimental model induces a rise in TAT complex levels and activates fibrinolysis [59].

The pattern is similar to that seen after TNF administration i.e. early fibrinolysis is initiated by a rise in t-PA levels and counteracted by a subsequent rise in PAI-1 levels resulting in a transient elevation of levels of PAP complexes and this is followed by sustained activation of coagulation [59]. Recombinant IL-1 receptor antagonist (IL-1ra) infused in patients with sepsis [60] and non-human primates with lethal bacteremia [59] can attenuate the coagulation response as assessed by TAT complex levels.

Although IL-1ra had an attenuating effect on the rise of t-PA and PAI-1 levels in the experimental bacteremic model, the early rise of PAP complex levels was not influenced [59]. Similarly, IL-1ra in septic patients had no effect on PAP levels [60]. Also anti-IL-6 monoclonal antibodies can significantly reduce the increase in levels of prothrombin fragment F1 + 2 and TAT complexes in non-human primates subjected to low dose endotoxin [43] but do not suppress plasmin generation [43, 45]. These studies indicate that TNF, IL-1 and IL-6 are involved in the activation of coagulation and TNF and IL-1 in the activation of fibrinolysis. There are however, very complex interactions between these various cytokines (and other mediators) and their role has not been completely elucidated. It has convincingly been shown that thrombin generation can activate fibrinolysis [61]. However, in a mild endotoxemia model prevention of thrombin generation by administration of a tissue factor neutralizing monoclonal antibody or direct neutralization of thrombin by continuous infusion of recombinant hirudin had no effect on activation of fibrinolysis [45]. In this model, therefore, induction of coagulation and fibrinolysis appears to be regulated independently [42-45]. It has been suggested that this also occurs in patients with sepsis [5].

Abnormalities in coagulation and fibrinolysis in patients with sepsis

In patients with severe sepsis signs of activation of coagulation and fibrinolysis as judged by changes in common hemostatic variables occur frequently. During the process of intravascular coagulation there is consumption of fibrinogen, reduction in platelet count and increases in prothrombin and activated partial thromboplastin times, changes that are most pronounced in DIC [3]. Activation of fibrinolysis results in various fibrin degradation products. The early dynamics of coagulation and fibrinolysis have been studied in patients with severe chemotherapy-induced neutropenia, who are prone to severe septic complications, allowing serial measurements of hemostatic variables before and during evolving sepsis [62, 63]. These studies have shown that at the onset of sepsis levels of factor VII activity and antigen rapidly decline, followed by a rise in prothrombin fragment F1 + 2 and TAT complex levels and associated with a rapid fall in ATIII activity [62]. Also, tPA antigen levels and PAI-1 activity and levels of PAI-1 antigen rapidly rise, associated with a decrease in α_2-antiplasmin activity and a rise in total fibrin(ogen) degradation products [63]. These changes were particularly seen in patients who progressed to septic shock. Al-

though this study concerned only neutropenic patients, which may limit generalization of the findings, it shows that the activation of coagulation and fibrinolysis are an early phenomenon in sepsis. Levels of factor VII are usually lowered in patients with severe sepsis [1, 3, 7, 62, 64] and levels of TAT complexes are elevated in the majority of these patients, even in the absence of clinical signs of DIC [4, 5, 27, 65-68]. Levels of most natural coagulation inhibitors are markedly lowered most likely related to consumption with an increased turnover during the coagulation process. ATIII levels are generally decreased during severe sepsis [1-4, 7, 27, 35, 62, 67]. The lowest levels are observed in septic shock [1, 62, 67] and they are sensitive markers of an unfavourable outcome [3, 62].

Serial measurements show a slow spontaneous recovery toward normal values in survivors, whereas levels usually remain low in non-survivors [1, 3, 4]. Also protein C concentrations are decreased in patients with severe sepsis [1-4, 7, 27, 35, 64, 67], a phenomenon which is most pronounced in septic shock even in the absence of clinically overt DIC [1, 67]. In nonsurvivors usually a severe and prolonged decrease in PC activity is observed, whereas in survivors serial measurements show a gradual return towards normal levels [1, 3, 4]. Although consumption of PC during the coagulation process is a major mechanism, also downregulation of thrombomodulin in endothelial cells may interfere with PC activation. In septic patients there is evidence that PC activity is also regulated by binding to PC inhibitor and α_1-antitrypsin, thereby forming complexes by which PC might loose its antithrombotic properties. Levels of PC inhibitors are decreased and these complexes appear in the circulation during sepsis [27].

Plasma concentrations of both total and free protein S may also be lowered, but usually less pronounced than the decrease of PC and ATIII [3, 7, 64]. On the other hand, levels of TFPI generally increase in sepsis [69, 70], and its kinetics apparently differ markedly from the kinetics of AT III, PC and PS in sepsis. Loss of activity of most of the inhibitors during the coagulation process may by itself contribute to a sustained procoagulant state.

The contact system consisting of the zymogens factor XII, factor XI, prekallikrein and the substrate procofactor high-molecular-weight kininogen, can also be activated during sepsis. This is demonstrated by the finding of low plasma levels of prekallikrein and factor XI and XII [1, 2, 68, 71] and elevated concentrations of complexes between kallikrein and its inhibitors C1-inhibitor and α_2-macroglobulin and between factor XIIa or XIa and C1-inhibitor [67, 71, 72]. Activation of this system, however, does not seem to be involved in coagulation activation, but rather contributes to the development of hypotension in sepsis by the release of the potent vasodilator bradykinin [17]. Also, activation of the contact system may activate the fibrinolytic system [36].

Activation of the fibrinolytic system in sepsis can be demonstrated by the presence of circulating PAP complexes which can be found in many patients [5, 65, 66]. Although levels of t-PA antigen are usually elevated in patients with severe sepsis [2, 4, 35, 63], t-PA-activity can often not be detected or is only mildly elevated [2, 35], indicating inhibition of t-PA activity, most likely by PAI-1.

Indeed, plasma levels of PAI-1 antigen [1, 4, 35, 73-76] and PAI-1 activity [2, 35, 63, 74] are strongly elevated in patients with the severe forms of sepsis. Although in uncomplicated sepsis PAI-1 levels may be in the normal range [1], in septic shock they are usually markedly elevated. In most studies high PAI-1 levels are highly predictive for an unfavourable outcome [1, 63, 73-75]. PAI-concentrations may be highest on admission to decline in the following days [75, 76] even in nonsurvivors [75], or remain elevated or even increase in nonsurvivors [1, 4, 74].

Levels of α_2-antiplasmin, another regulator of plasmin activity and therefore fibrinolysis, may be in the normal range [1, 2, 4] or are decreased [1, 67, 75-77]. Low concentrations are particularly observed in patients with septic shock [1, 63, 76] indicating a stronger activation of fibrinolysis in the more severe forms of sepsis. In conclusion, coagulation and fibrinolysis are usually activated in patients with sepsis and this is most pronounced in septic shock. However, fibrinolysis is strongly inhibited creating a dysbalance between coagulation and fibrinolysis resulting in a procoagulant state in sepsis which may contribute to the development of organ failure and mortality.

Dysbalance between coagulation and fibrinolysis

As discussed before, studies in human endothelial cells have shown that endotoxin can, directly or indirectly through the actions of TNF and IL-1, stimulate the procoagulant properties of vascular endothelium in vitro and reduce its anticoagulant properties: enhancement of tissue factor expression, downregulation of proteins C and S. In addition, endotoxin, TNF and IL-1 suppress the fibrinolytic capacity of vascular endothelial cells mainly by stimulation of PAI-1 production and release.

In human volunteers and non-human primates challenged with either a low dose endotoxin or TNF early activation of fibrinolysis is observed before significant thrombin generation can be detected, and fibrinolysis is already offset by the release of PAI-1 when thrombin generation becomes maximal. Thus, there is a remarkable dysbalance between activation of coagulation and fibrinolysis creating a procoagulant state several hours after the challenge, which is also observed in non-human primates infused with (sub)lethal dose of live E. coli microorganisms. In septic patients coagulation and fibrinolysis are activated with subsequent strong inhibition of fibrinolysis which may explain why TAT levels are usually more elevated than PAP levels [5, 78]. The (dys)balance between coagulation and fibrinolysis can be assessed by the ratio of levels of TAT and PAP complexes. In many patients with severe sepsis the TAT/PAP ratio is increased, reflecting a procoagulant state [5, 65, 66]. Septic patients with organ dysfunction have higher TAT/PAP ratios than those who do not develop organ dysfunction [5]. Moreover, the rise of the TAT/PAP ratio may precede the development of organ dysfunction. Also, the TAT/PAP ratio is higher in nonsurvivors than in

survivors of a septic insult [5, 65]. These observations suggest that this dysbalance contributes to the development of organ dysfunction and to mortality. A positive correlation between the TAT/PAP ratio and PAI-1 levels also suggests that impaired fibrinolysis is the most important mechanism for this dysbalance [5]. Also at the local levels in the lungs, enhanced coagulation and suppressed fibrinolysis, as assessed in broncho-alveolar lavage fluid has been found in patients with ARDS and this dysbalance may be an important factor in the pathogenesis of ARDS which is a common complication of sepsis [79, 80]. In conclusion, in sepsis a dynamic process of coagulation and fibrinolysis is ongoing with a dysbalance between coagulation and (impaired) fibrinolysis. These abnormalities have major pathophysiological and therefore clinical implications as the fibrinolytic capacity to counteract widespread vital organ microvascular thrombosis becomes insufficient which seems to contribute to the development of (multiple) organ failure and mortality.

Therapeutic implications

The current treatment of DIC in sepsis includes vigourous treatment of the underlying infection and supplementation of clotting factors (fresh frozen plasma) and platelets when considered necessary. As there are no controlled clinical trials which have demonstrated superiority of any therapeutic regimen, additional therapy in case of clinically important thromboembolic or bleeding complications is difficult and usually guided by clinical judgement. Heparin has been widely used to block coagulation in conjunction with supplementation of clotting proteins, but its use is still controversial, although most authors advise to administer heparin in low-dose continuous infusion [18]. In an experimental sepsis model heparin could ameliorate organ damage [81] but there is no evidence that this also occurs in human sepsis. Experimental studies have not shown that heparin can alter the shock response or lethal effects of E. coli infusion although it is effective in blocking the DIC response [82]. Since the inhibitors of coagulation are consumed during the process of coagulation, substitution of these inhibitors may be a therapeutic option. Numerous anecdotal reports have shown promising effects of substituting the acquired ATIII deficiency in sepsis with infusion of ATIII concentrates. High dose of ATIII given before infusion of a lethal dose of E. coli in baboons could reduce the intensity of both coagulopathic and cell injury responses and prevent death [30, 83]. Randomized clinical studies in patients with DIC demonstrated a significant attenuation of DIC after ATIII treatment [84, 85]. Only one study, however [84], included patients with trauma or sepsis and no placebo-control group was included. The only published double-blind placebo-controlled trial of ATIII was performed in patients with septic shock [86]. This study showed that the duration of DIC was reduced in the ATIII-treated group and mortality was reduced by 44% although this did not reach statistical significance. A large-scale clinical trial is necessary

in order to establish whether treatment with ATIII is effective. ATIII has not only antithrombotic properties but may also have an effect on the inflammatory response. In cultured endothelial cells ATIII can promote prostacycline release which may inhibit cytokine release and may have an effect on activated leukocytes [87]. Thus, ATIII may have an additional protective effect.

Activated protein C can prevent in the baboon model the coagulopathic, hepatotoxic and lethal effects of infusion of lethal doses of live E. coli [31]. Preliminary studies of protein C substitution in a small series of patients with DIC, albeit not related to sepsis, have shown promising results [88].

In experimental septic models infusion of TFPI reduces the coagulation response and diminishes cell injury and also significantly reduces the rise in IL-6 levels, suggesting also an effect on the inflammatory response [32, 33]. Also mortality is largely prevented. The clinical effects of TFPI are now being evaluated in a phase II clinical trial in patients with sepsis.

In addition to substitution of inhibitors of coagulation, interference with cytokine activities may be another therapeutic strategy. Although highly effective in the animal model, large scale clinical trials in septic patients using several of such strategies have provided disappointing results concerning the effects on mortality [10, 11, 13] but effects on coagulation abnormalities have not been reported in detail. In one study using an anti-TNF monoclonal antibody no effect was observed on coagulation and fibrinolysis variables [89]. New strategies more specifically aimed at treatment or prevention of DIC in sepsis may include inhibition of coagulation factor activity e.g. by anti-tissue factor antibodies [15, 90] or anti factor VIIa antibodies [16]. It may be expected that the increased knowledge of the pathophysiology of coagulation and fibrinolysis will ultimately result in effective therapeutic modalities for septic patients.

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EXPERIMENTAL AND CLINICAL APPROACH

Therapies Directed against TNF-α and IL-1 during Sepsis

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Sepsis is a systemic inflammatory response to an infectious stimuli [1]. Sepsis is diagnosed when clinical and/or laboratory parameters confirm the presence of an inflammatory response and identifies an infection as the cause of this response. The infection can be located in any organ or tissue of the body and can be caused by bacteria, fungi, parasites or viruses. Sepsis has been documented in all age groups and may occur both in immunocompetent and immunosuppressed patients. Although our understanding of the pathophysiology of sepsis has improved considerably and despite availability of modern medical technology, the morbidity and mortality associated with this syndrome has not been much affected in the last decade [2, 3].

Sepsis begins when infections cannot be contained within tissues and infectious agents or toxins invade the blood stream and cause a profound systemic inflammatory reaction. This reaction involves cells (neutrophils, macrophages, monocytes and endothelial cells), plasma factors (complement and coagulation system), and products of cells (cytokines, eicosanoids, nitric oxide etc.) [4-8]. These various components of the inflammatory response are important in gauging the inflammatory response to the magnitude of the infectious stimuli and have complex interrelationships and interactions with both potentiating and inhibiting effects [9]. Excessive amounts of these mediators, however, can cause vascular paralysis, increased vascular permeability, myocardial depression, renal failure, respiratory failure, encephalopathy, coagulation abnormalities, and, when untreated or untreatable, can lead to death. Thus host inflammatory mediators play a central role in the pathogenesis of sepsis-associated morbidity and mortality.

Conventional therapy of sepsis consists of eradication of infections with antibiotics, elimination of septic foci with surgical procedures, and supportive intensive care management of organ failure. Since inflammatory mediators are instrumental in sepsis-associated organ dysfunction, much research has focused on modulating the host inflammatory response as an adjunctive therapeutic option in sepsis. Most of this research has focused on inhibiting components of the host inflammatory response with appropriate antibodies or receptor antagonists.

The cytokines, peptides that regulate the amplitude and duration of the host inflammatory response, are an important group of inflammatory mediators [9].

Tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8) are cytokines often associated with sepsis. These cytokines are released from various cells (monocytes, macrophages, endothelial cells, etc.) in response to infectious stimuli and bind to specific receptors of other cells changing their behavior and defining their role in the inflammatory response. During infection and inflammation, the host not only produces cytokines with predominantly pro-inflammatory properties, it also produces counter-inflammatory cytokines like interleukin-10 (IL-10) and IL-4 and soluble receptors or receptor antagonists of pro-inflammatory cytokines [9-13]. Among other factors released during the inflammatory response to infections are bioactive phospholipids such as platelet activating factor (PAF) [14].

Tumor necrosis factor alpha

TNF-α, a 17-kDa polypeptide produced primarily by mononuclear phagocytes, is implicated in the pathogenesis of sepsis [15]. Administration of endotoxin in humans leads to an early and substantial increase in TNF-α levels [16] TNF-α challenge in dogs simulates many abnormalities and systemic manifestations of human sepsis [17]. Inhibition of TNF-α with appropriate antibodies improves survival in animal models of bacteremic and endotoxic shock [18, 19]. Lastly, TNF-α has been detected in the blood of septic patients [20, 21]. Because of these findings, clinical trials were conducted to test whether inhibiting TNF-α can also improve survival in human sepsis. The trials were conducted with various TNF-α neutralizing agents such as monoclonal antibodies or antibody-fragments directed against TNF-α or with soluble TNF-α-receptors with neutralizing capabilities.

Trials with murine monoclonal antibodies

In a phase II study, the efficacy of three doses (ranging from 0.1 to 10 mg/kg) of a murine monoclonal antibody against TNF-α (CB0006) [22] was studied in 80 patients with severe sepsis or septic shock. No overall 28-day survival benefit was found although patients with high TNF-α levels seemed to have some benefit from the 10 mg/kg antibody treatment. More than 900 patients with sepsis or septic shock were included in a multicenter North American study [2] which used three different concentrations (0, 7.5, and 15 mg/kg) of a murine monoclonal antibody to TNF-α. This trial found no overall reduction in 28-day mortality among the three groups. A second international trial [23] with the same antibody used three concentrations (0, 3, 15 mg/kg) and enrolled over 500 patients in septic shock patients. This trial too failed to show any significant effect of the antibody on 28-day survival in septic shock patients as compared to controls.

Human or humanized monoclonal antibodies

In a multicenter dose-ranging study, Reinhart et al. [24] used a monoclonal antibody fragment directed against TNF-α in patients with severe sepsis or septic shock. This trial enrolled over 120 patients but also failed to show any beneficial effects of the antibody fragment on 28-day survival. A post hoc analysis of this trial suggested that patients with baseline increased IL-6 concentrations (greater than 1000 pg/ml) may have had some benefit from the drug. This hypothesis was tested in a prospective randomized study but was stopped because it also failed to reduce sepsis-associated mortality (personal communication). The American arm of this study however is still ongoing because an interim analysis of this trial did not urge to stop this trial due to futility.

Fusionproteins

Three doses of a soluble fusion protein (p75 kd TNF-α receptor and Fc portion of IgG1) [3], which binds and neutralizes TNF-α, were used in patients with severe sepsis. In this study, mortality increased with increasing doses (0.15, 0.45, and 1.5 mg/kg) of the fusion protein. In a most recent study [25], yet another soluble fusion protein (RO 45-2081; p55 TNF-α receptor and portion of IgG1), was studied in septic patients. The study used three different doses of the fusion protein and included several hundred patients. In this study, as in previous studies, overall survival was not significantly different among the groups studied, however the subgroup of patients with severe sepsis and early septic shock may have had benefit.

These negative results question the rationale of therapies directed against TNF-α.

However, antibodies directed against TNF-α have proven clinical efficacy in special groups of patients with infectious disease. Antibiotic therapy of patients with relapsing fever (*Borrelia recurrentis* infection) is followed by fever, persistent hypotension, and rigors (Jarisch-Herxheimer reaction). This response is associated with increases in circulating cytokine (TNF-α, IL-6, IL-8) levels. Pretreatment with antibodies against TNF-α suppressed the Jarisch-Herxheimer reaction and reduced circulating cytokine levels in these patients [26].

Interleukin-1

The term IL-1 is used for both IL-1α and IL-1β, both produced by mononuclear cells and sharing similar biological properties [27]. Infusion of IL-1 simulates symptoms of sepsis [27] and endotoxin administration in humans causes elevation of IL-1 levels [28]. In addition, IL-1 is detected in serum of patients with sepsis or septic shock [29-31]. IL-1 has a naturally occurring receptor antagonist (IL-1ra) which has been used in laboratory and clinical trials to inhibit IL-1 ac-

tivity. In laboratory animals, IL-1ra was highly efficacious in increasing survival during both endotoxemic and bacteremic shock [32, 33]. The foregoing discussion was the rationale behind using recombinantly IL-1ra to decrease the morbidity and mortality of human sepsis.

Clinical trials of IL-1ra in sepsis

In an initial clinical trial [34] 99 patients with sepsis received either IL-1ra (Synergen Inc, Boulder, CO, USA) – in three dose ranges – or placebo. The study found not only that the drug was well tolerated but also demonstrated a dose-related improvement in 28-day survival. This improvement was accompanied by decreases in severity of injury score (APACHE II) and decreases in IL-6 concentrations (within the first 24 hours). However, a second trial [35] of IL-1ra which enrolled over 800 septic patients, failed to show efficacy and did not improve 28-day survival when compared to a control group. Since this trial suggested improved survival in a subgroup of patients with one or more organ failures, a new trial was started which enrolled patients with characteristics of the subgroup which seemed to benefit from IL-1ra treatment. However, this trial too failed to show clinical efficacy [36].

Why clinical trials directed against TNF-α and IL-1 may have failed

Some of many possible reasons of why these promising immunomodulatory therapies of sepsis have failed may be as follows:

1. Mediators involved in the pathogenesis of sepsis have both beneficial and deleterious effects. For example, TNF-α is a cytokine which is important in regulating host defense mechanisms. For example, TNF-α promotes transendothelial migration of neutrophils to sites of inflammation and infection [37] and promotes superoxide production of neutrophils which is important in killing bacteria [38]. Rats pretreated with recombinant TNF-α one week prior to abdominal infection through cecal ligation and puncture all survived whereas mortality was 50% in rats not pretreated with TNF-α [39]. Furthermore, inhibiting TNF-α activity in *Listeria monocytogenes* infections has worsened outcome [40]. These and other studies [41] underline the importance of TNF-α in acute bacterial infections. Likewise, other "mediators of sepsis" have important functions within the specific and non-specific host defense to infections.
2. One important idea behind directing therapies against these mediators was that their excessive release during severe infections leads to the severe systemic manifestations of sepsis. Although overwhelming release of pro-inflammatory mediators may contribute to the septic response, a massive compensatory anti-inflammatory reaction which occurs concomitantly seems to be also important in the development of sepsis [9, 11-13].

3. The patient population included in these trials were very heterogeneous. Age, immune status, and genetic predisposition may all alter the inflammatory response to infections and lead to different responses to anticytokine therapies. In one experimental model [42], for example, older animals were ten times more sensitive to endotoxin administration than younger animals and released more TNF-α and more nitric oxide in response to endotoxin than younger animals. Genomic polymorphism within the TNF-α gene locus may also influence plasma TNF-α levels during sepsis and influence subsequent survival or non-survival of patients [43]. These studies show the importance of patient characteristics in the immune response to infections and suggest that these differences may also lead to different responses during immunomodulatory therapies.
4. The criteria used in enrolling patients in immunomodulatory trials may be important when diagnosing sepsis as a clinical syndrome but may not be predictive of the patients immune status. We may need immunologic parameters such as HLA-classification, circulating cytokine levels, or new parameters like procalcitonin [44] which better identify subgroups of septic patients who may benefit from pro- or anti-inflammatory therapies.

In conclusion, despite the implication of TNF-α and IL-1 in the pathogenesis of sepsis and sepsis-associated organ failure, therapies directed against these cytokines have failed to show clinical efficacy. Future studies may have to better identify circumstances under which these therapies may become an adjunctive therapeutic option in septic patients.

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Effects of Adrenergic Agents on the Hepato-Splanchnic Circulation: An Update

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Recent studies [1, 2] have implicated the hepato-splanchnic area in the development of multiple organ failure. Important alterations can take place in the gut and the liver during sepsis. A decreased gastric intramucosal pH (pHi), thought to reflect inadequate gut perfusion, is often encountered in sepsis and is associated with increased mortality rates [3, 4]. Liver dysfunction is also common in sepsis and alterations in liver blood flow may contribute to it. The hepatic venous oxygen saturation (ShO_2) is often decreased [5-9], reflecting an imbalance between oxygen demand and supply in the hepato-splanchnic area. Also, the liver could be a major source of cytokine release [10], possibly triggered by hypoxia.

Several mechanisms have been implicated in these disturbances in the hepato-splanchnic area. First, blood flow could be diverted away from the splanchnic area in order to preserve blood flow to the heart and the brain. Second, the splanchnic region contributes to a larger fraction of total body oxygen consumption in septic patients [6, 11]. In particular, liver metabolism is increased out of proportion to the increase in liver blood flow so that ShO_2 is usually decreased [5, 6, 12, 13]. Finally the gut mucosa could be more sensitive to a reduction in blood flow. The countercurrent exchange mechanism promotes O_2 diffusion between the artery and the vein at the base of the villus so that the top could be deprived of O_2. Hence the hepato-splanchnic area could be more sensitive to blood flow alterations in sepsis. Vasoactive agents could further interfere with the oxygen balance in the hepato-splanchnic area, increasing oxygen demand, and altering the distribution of blood flow within or between organs.

We will briefly review recent data, both in animals and in humans, to better understand the effects of various vasoactive agents on the hepato-splanchnic area.

Effects of dopamine

Dopamine has been proposed to increase hepato-splanchnic blood flow through activation of the dopaminergic receptors [14-17]. Several studies have confirmed that dopamine can increase hepato-splanchnic blood flow in critically ill

patients. Ruokonen et al. [9] observed that dopamine administered to increase mean blood pressure to 70 mmHg, significantly increased hepato-splanchnic blood flow and oxygen consumption ($\dot{V}O_2$). Nevertheless, there were substantial interindividual variations. On the contrary, Maynard et al. [18] did not observe any significant change in hepato-splanchnic blood flow during dopamine administration in critically ill patients. More recently, Meier-Hellmann et al. [17] studied the effects of low-dose dopamine (2.5-3.0 mcg/kg.min) in patients with hyperdynamic septic shock already treated with norepinephrine. Dopamine selectively increased hepato-splanchnic blood flow in patients in whom the ratio between hepato-splanchnic blood flow and cardiac index was lower than 0.3, but did not alter blood flow in the other patients.

Recent studies have questioned the role of dopamine on the microcirculation. Segal et al. [19] observed that dopamine administration in pigs hastened the onset of gut hypoxia during reductions in blood flow. However, Germann et al. [16] reported in a hyperdynamic porcine endotoxic shock model that dopamine, administered at doses of 2.5, 5, 10 and 20 mcg/kg.min, increased gut mucosal PO_2 in a dose dependent manner. The effects on mucosal blood flow, estimated by pHi measurements, were also variable. In septic patients, Marik and Mohedin [20] reported that dopamine, administered to restore arterial pressure, decreased pHi. Also Olson et al. [21] observed that low dose dopamine administration did not change pHi. Finally, Nevière et al. [22] reported that 5 mcg/kg.min dopamine decreased gut mucosal blood flow measured by laser Doppler technique but did not significantly alter pHi.

In summary, hepato-splanchnic blood flow remains unchanged or increases during dopamine administration while mucosal blood flow and pHi decreases or, at best, remains unchanged.

Effects of norepinephrine

The data concerning norepinephrine are scarce. Norepinephrine is a catecholamine with predominant alpha but also beta adrenergic effects. In hypodynamic septic animals, norepinephrine altered mesenteric perfusion, principally through an alpha-adrenergic effect [23]. However, in a fully fluid resuscitated endotoxic shock model in the dog, Zhang et al. [24] observed that norepinephrine increased mesenteric and hepatic blood flow. Furthemore, norepinephrine increased oxygen extraction capabilities so that the liver critical DO_2 was decreased [24]. These effects seem to be due more to the beta- than alpha-effects since phenylephrine, a pure alpha-agonist agent, did not alter oxygen extraction capabilities and critical DO_2 [25].

In septic patients, Ruokonen et al. [9] reported that norepinephrine administration increased hepato-splanchnic blood flow and $\dot{V}O_2$. However, the effects of norepinephrine on splanchnic blood flow were not uniform. Recently, Meier-Hellmann [26] reported that hepato-splanchnic DO_2 and $\dot{V}O_2$ was higher in pa-

tients with septic shock treated with norepinephrine than in patients with severe sepsis. However, the pHi was similar in both groups of patients. In a prospective study, Marik and Mohedin [20] observed that norepinephrine, administered in order to restore blood pressure in hypotensive septic patients, increased pHi. These results await confirmation, since to our knowledge, no other prospective study has analyzed the effects of norepinephrine on pHi.

Effects of epinephrine

At low doses, epinephrine has a predominant beta-1 and beta-2 adrenergic effect while at moderate and high doses the alpha-1 vasoconstrictor effect predominates.

In patients with septic shock, Meier-Hellmann et al. [7] demonstrated that changing the catecholamine regimen from a combination of dobutamine and norepinephrine to epinephrine alone increased the gradient between mixed venous and hepatic venous O_2 saturations. These authors also reported that fractional blood flow and pHi decreased while hepatic venous lactate increased. Using a similar study design, Levy et al. [27] reported that epinephrine increased arterial lactate levels and decreased pHi in septic patients. However, these effects were transient. Thus the data, although scarce, consistently demonstrate a deleterious effect of epinephrine on hepato-splanchnic blood flow and metabolism, at least transiently.

Effects of dobutamine

In control conditions, beta adrenergic agents usually increase mesenteric and hepatic blood flow [28, 29]. This effect is preserved in septic animals. Fink et al. [30], observed that dobutamine increased mesenteric blood flow and prevented alterations in ileal permeability and acidosis without influencing gut $\dot{V}O_2$. However, these effects were observed with high doses of dobutamine. In a model of hyperdynamic endotoxic shock in the dog, De Backer et al. [31] observed that dobutamine at doses of 5 and 10 mcg/kg.min increased mesenteric DO_2 and prevented the increase in ileal PCO_2 gap. Interestingly the effects of dobutamine were similar at the dose of 5 and 10 mcg/kg.min. Recently, in another model of endotoxic shock in the pig, Nevière et al. [32] also observed that a 5 mcg/kg.min dobutamine infusion increased gastric mucosal blood flow and limited the increase in mucosal-arterial PCO_2 difference. De Backer et al. [33] also observed that dobutamine at doses of 5 and 10 mcg/kg.min increased total liver DO_2, $\dot{V}O_2$ and lactate consumption. This increase in liver blood flow and metabolism was accompanied by an increase in hepatic venous oxygen saturation suggesting an improved balance between oxygen supply and demand. Webb et al. [34] and Tighe et al. [35] observed that dobutamine altered liver ultrastruc-

ture in a porcine model of fecal peritonitis but portal blood flow was not increased by dobutamine in this model.

A number of investigators have studied the effects of dobutamine on splanchnic perfusion in septic patients [13, 22, 33, 36-39]. Although pHi remained stable in some studies [13, 39], most authors observed an improvement in pHi during dobutamine administration in septic patients [22, 36-38]. Silverman et al. [37] reported that pHi increased in septic patients with a low baseline pHi, but remained stable in septic patients with a normal pHi. Gutierrez et al. [36] reported increases in pHi and Nevière et al. [22] increases in gastric mucosal blood flow, measured by laser Doppler. Hepato-splanchnic blood flow, measured by the indocyanine green clearance technique, increased in hemodynamically stable [33] as well as unstable [13] septic patients. This effect was associated with significant increases in hepato-splanchnic DO_2 and $\dot{V}O_2$ [33].

In summary, experimental and clinical studies indicate that dobutamine administration consistently increases hepato-splanchnic blood flow and usually increases pHi.

Effects of dopexamine

Dopexamine combines beta-2, some beta-1 and dopaminergic adrenergic receptor agonist activity without any alpha-agonist activity. Several experimental studies have demonstrated that dopexamine can improve gut oxygenation. In rabbits with septic shock, Lund et al. [40] reported that dopexamine increased liver and gut mucosal tissue PO_2. In another study [41], gut lactate production could be reversed during dopexamine administration in endotoxemic dogs. Moreover, Webb et al. [34] and Tighe et al. [35] observed that dopexamine preserved liver ultrastructure in a model of fecal peritonitis in pigs.

In critically ill patients, dopexamine increased hepato-splanchnic blood flow determined by indocyanine green clearance and monoethylglycineexylidide (MEGX) formation [18, 42]. However, the effects of dopexamine on pHi have been inconsistent, since pHi increased in some studies [18, 42] but not all [43, 44].

Hepato-splanchnic $\dot{V}O_2/DO_2$ relationships

The use of hepatic vein catheterization offers the opportunity to investigate regional $\dot{V}O_2/DO_2$ relationships by measuring hepato-splanchnic blood flow and hepatic venous oxygen saturation (ShO_2). In 42 hemodynamically stable septic patients, we [45] studied the effects of dobutamine at a rate of 5 and 10 mcg/kg.min on hepato-splanchnic DO_2 and $\dot{V}O_2$. Hepato-splanchnic $\dot{V}O_2$ in-

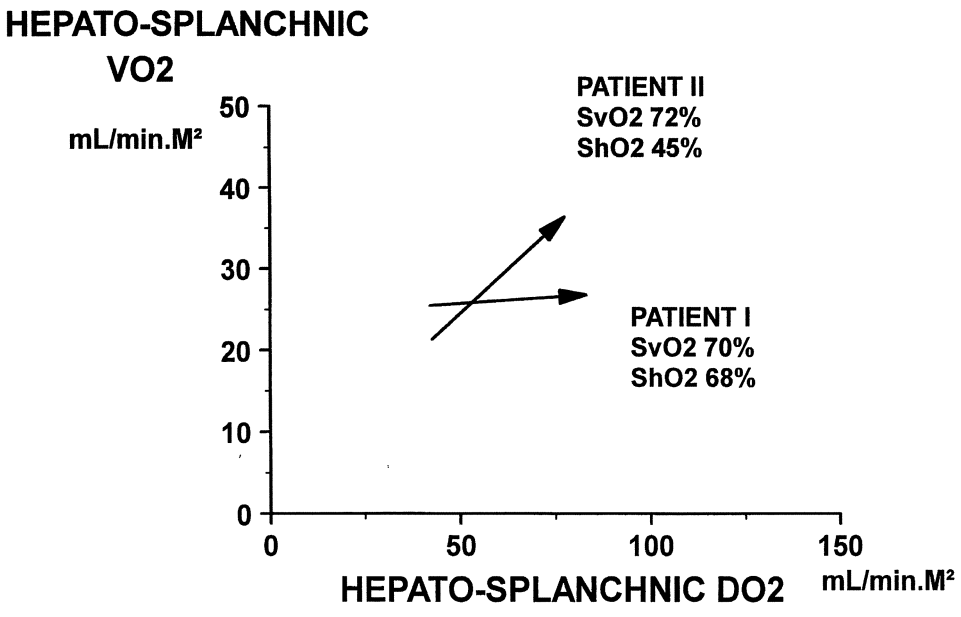

Fig. 1. Example of hepato-splanchnic $\dot{V}O_2/DO_2$ relationships in 2 patients

creased only in patients with an increased gradient between SvO_2 and ShO_2, even though dobutamine similarly increased in hepato-splanchnic DO_2 in the 2 groups (Fig. 1). Also the slope of the hepato-splanchnic $\dot{V}O_2/DO_2$ relationship was inversely related to the difference between SvO_2 and ShO_2. On the contrary, the response in global hemodynamic parameters was similar in both groups. These results suggest that hepato-splanchnic $\dot{V}O_2/DO_2$ dependency could be observed in some septic patients even when they appear hemodynamically stable. Similarly Steffes et al. [12] observed that red blood cell transfusions increased hepato-splanchnic $\dot{V}O_2$ in some septic patients but they did not attribute these changes to $\dot{V}O_2/DO_2$ dependency since splanchnic lactate consumption remained stable. However, the interpretation of splanchnic lactate consumption is very difficult in patients since it represents the balance between gut lactate production and liver lactate consumption, and these parameters could be affected differently by the various interventions. Recently, Reinelt et al. [46, 47] observed that the change from norepinephrine to phenylephrine, depriving these patients of beta adrenergic stimulation, reduced hepato-splanchnic DO_2 (from 182 ± 40 to 124 ± 21 ml/min.M^2, $p < 0.05$) and $\dot{V}O_2$ (from 80 ± 15 to 69 ± 11 ml/min.M^2, p = ns), but also reduced lactate consumption by the liver directly assessed by stable isotopes (from 603 ± 292 to 420 ± 164 mcM/min.M^2). This suggests that $\dot{V}O_2/DO_2$ dependency occurred in these patients.

Conclusions

Hepato-splanchnic hemodynamics can be significantly altered in septic patients, as indicated by decreased ShO_2 and pHi, and, possibly in some cases, hepato-splanchnic $\dot{V}O_2/DO_2$ dependency. The effects of the different catecholamines on hepato-splanchnic blood flow are variable and can not be inferred from the evaluation of global hemodynamic parameters.

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When to Operate or to Stop Operating and to Plan a Reoperation

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The indications for an operative procedure have remained much the same for a number of years, but there are now several new indications for considering an operation and particularly for considering a reoperation. The usual indications for an elective operation must consider the risks versus the benefits. For emergency operations the consideration must be whether or not the procedure is life-saving and, again, risks versus benefits related to the procedure. What is the risk for the patient, what are the potential benefits, and do they balance out as a win-win situation for the patient and his or her family?

In recent years some of the usual indications for operation have been clouded because of end-of-life considerations and deterioration with the aging process such as with Alzheimer's disease. In the United States this is particularly evident for patients with Alzheimer's disease, severe senility, or total incapacity who live in a nursing home, who do not recognize anyone, do not know their families and are living a vegetative existence. If they develop a life-threatening problem, which could be taken care of by an operation, is it ethical and is it moral to carry out such a procedure and to make them suffer through it even though they are going to go back to the same vegetative state that they were in before? The fact that we can do an operation for an acute condition in such a patient does not necessarily make it right or necessary. I have observed elderly patients who were categorized as "Do Not Resuscitate" immediately after an emergency or urgent operation. Can we propose "Do Not Resuscitate" preoperatively and avoid an operation that will not improve the patient's quality of life? These are tremendous ethical dilemmas for surgeons taking care of such patients.

Another consideration in risks versus benefits is with minimal operations. Laparoscopy and thoracoscopic procedures now can be done at less risk for an individual. For example, a post-traumatic hemothorax can be taken care of thoracoscopically, avoiding a full formal thoracotomy. The same is true for empyema. The need for an abdominal exploration after trauma in stable patients with no specific indications for operation may be evaluated by a diagnostic laparoscopy. Staging of abdominal malignancy and the question of an acute abdomen also could be determined with minimal surgical procedures.

They greatly reduce the risk for the operation and increase the potential benefit for the patient.

There are now new indications for operation and/or reoperation which fall into two categories. First, there are intensive care unit patients who may or may not have had a previous abdominal procedure because of trauma or an acute abdominal problem. These patients, in the ICU, may be stable initially, but begin to develop remote organ failure or worsening of organ function which could be called MODS (multiple organ dysfunction syndrome). In such a situation there may be very specific and real indications for operation or reoperation to try to find a septic focus, an area of necrosis, or some other problems in the peritoneal cavity which is causing the remote organ deterioration [1, 2].

Secondly, postoperative patients or patients with bowel obstruction who have distention may have alterations in organ function based upon a great increase in intraabdominal or intraperitoneal pressure. This has been known for quite some time but it has not always been considered an important problem. Now this has been called the abdominal compartment syndrome [3, 4]. It is a very important consideration in patients with severe abdominal distension and potential increase in pressure and a related decrease in organ function within the peritoneal cavity.

There are now two major reasons for stopping an operation and planning on a reoperation sometime later. The first reason is with abdominal trauma and major organ injury with considerable blood loss. If the patient develops acidosis, hypothermia and a coagulopathy (usually associated with blood loss and multiple blood transfusions) there may be blood oozing from everywhere which cannot be controlled. In such a situation it is now recognized that persistence in trying to correct this situation during the operation in the operating room with the abdomen and/or the chest open will not be successful. However, rapid conclusion of the operation, bringing the abdominal wall together or using a silo, and taking the patient to the intensive care unit, may allow rewarming the patient and correction of the acidosis and coagulopathy. Then the patient can be taken back to the operating room for a definitive conclusion of the procedure. Trauma centers and trauma surgeons now recognize this possibility and it is a major reason for stopping an operation and planning on a reoperation soon after the patient stabilizes in the intensive care unit [5].

The second reason for stopping an operation and planning on a reoperation is for a patient with generalized peritonitis where reoperation is necessary to break up foci of contamination, intraloop infection and the prevention of residual abscesses. It is recognized that residual infection may not be preventable at the initial operation no matter how long one persists in working within the septic peritoneal cavity [1, 6].

These new approaches will be reviewed in detail as to the present standing, indications, techniques and results. These approaches have led to improved pa-

tient care and better survival for a number of patients after illness and/or operation or trauma.

Abdominal exploration for remote organ dysfunction or failure

When I first described multiple organ failure problems, I used several examples of patients who had died with multiple organ difficulties [7]. One of these patients had a colon anastomosis which leaked and caused generalized peritonitis – this is classic sepsis. Another patient had acute hemorrhagic pancreatitis, deteriorated and died rather quickly with what was a fairly pure inflammatory process. A third patient had a low cardiac output after a double heart valve replacement and died, in essence, of a low output and organ ischemia. Thus we know that these factors – sepsis, inflammation, ischemia, gangrene and necrosis – can all contribute to multiple organ failure by mounting an inflammatory process which then becomes dangerous.

Early on with multiple organ failure it was recognized that in many patients sepsis, peritonitis or inflammation was a major cause of the difficulty. This is particularly true with reports from institutions that had a high level of penetrating abdominal trauma and other problems of acute abdominal inflammatory or infectious diseases. It was recognized then that if a patient with such a problem had an immediate operation, all the recognized abnormalities were corrected, and then the patient stabilized in the intensive care unit, all seemed to be going well. If, however, following a period of stabilization, the patient then began to experience difficulty with organ function, then there must be a recognized problem elsewhere. An example would be in a patient being supported by mechanical ventilation who is stable, has not improved definitely but also whose pulmonary function has not deteriorated. Such a patient then begins to develop worsening respiratory function with a requirement for a higher FiO_2 or other problems attendant to ventilation, then one must think seriously about an infectious process elsewhere. Remote organ dysfunction with sepsis elsewhere was described by Polk et al. [2]. They recognized that, if this occurred, there should be a "blind laparotomy" reoperation immediately and, in at least half of the patients, something would be found that could be corrected and the patient would improve and survive. Now, with diagnostic possibilities, including ultrasound, CT scans, and other studies of the chest and peritoneal cavity, such a blind reoperation should not be necessary.

The problems that could produce remote organ dysfunction include acute acalculous cholecystitis, bowel ischemia, abscesses in the pelvis, subphrenic region, subhepatic region, intraloop abscesses or retroperitoneum and finally bowel or gut perforation [1]. These and other problems, such as pancreatitis, can produce an inflammatory process and mediator release which induces organ damage and functional deterioration. These patients would have the setting of elevated temperature and increased white count. They would look septic and

they would have other problems as well with a mass or collection problem identified. The most important concept, however, is to recognize remote organ deterioration which may be caused by trouble within the peritoneal cavity [8].

A number of investigators have provided evidence for establishing the diagnosis of continuing abdominal sepsis by the presence or development of multiple organ failure. Ferraris found that the most significant predictor of continuing intraabdominal infection was unexplained single organ failure [9]. Others have found that early operation in organ failure improved survival whereas delayed operation furthered the peritonitis and worsened the prognosis [10, 11]. If, however, multiple organ failure has developed and then the focus of infection or necrosis is removed, organ function may not improve or return [12, 13]. This emphasizes the need for early identification of contributing factors.

The abdominal compartment syndrome

There is a long history of study in animals and people about the effects of increased intraabdominal pressure on organ function and on the circulation. However, little was done about this clinically for many years. One of the earliest studies was one by Thorington and Schmidt in 1923 on urinary output and blood pressure changes resulting from experimental ascites [14]. They found, for example, that a rise in intraabdominal pressure to 30 mmHg was uniformly followed by complete suppression of urine output in dogs and an increase in vena caval pressure. Thus, concern about intraabdominal pressure began with studies in cirrhotic patients and animals with ascites [15, 16] and with the development of the G suit for the prehospitalization treatment of shock by the United States military. The effect of increased intraabdominal pressure on renal function in man was studied by Bradley and Bradley in 1947 [17]. They found that effective renal plasma flow and glomerular filtration rate were reduced by increased abdominal pressure along with reduced dye excretion. Massive ascites could produce obstruction of the inferior vena cava. This was also implicated in the hepatorenal syndrome with cirrhosis [16]. The first report of renal failure from increased intraabdominal pressure in patients was by Richards et al., in 1983 [18]. They reported acute renal failure developing in four patients in association with increased intraabdominal pressure from postoperative hemorrhage. Operative decompression of the abdomen resulted in polyuria and resolution of the renal failure. This was followed in 1984 by the measurement of intraabdominal pressure as a criterion for abdominal reexploration by Kron et al. [19]. Abdominal pressure was measured by a manometer connected to a Foley catheter in the urinary bladder. They found a correlation between intraabdominal pressures above 25 mmHg and renal dysfunction and reported pressures above a 30 mmHg, resulting in oliguria in 11 postoperative patients. They recommend reexploration and decompression of the abdomen if pressure rose to 25 mmHg. This was first called the intraabdominal compartment syndrome in 1989 by Fietsam et al. [3].

There have also been numerous studies in animals of the effects of increased intraabdominal pressure on the circulation, on venous return, renal function, left ventricular performance, regional blood flow, microcirculatory blood flow in the gut, mucosal blood flow, and blood and tissue oxygen [20-25]. One of the mechanisms of action of increased abdominal pressure may be upregulation of plasma renin activity and aldosterone levels [26]. Increased intracranial pressure has also been described with increased abdominal pressure as has pulmonary dysfunction [27]. The physiological consequences of elevated intraabdominal pressure were described by Schein et al., in a collective review in 1995 [4]. These include an increase in heart rate, an increase in capillary wedge pressure, an increase in peak airway pressure, central venous pressure, thoracic pleural pressure, inferior vena cava pressure, renal vein pressure, and systemic vascular resistance. There is decreased cardiac output and decreased venous return, visceral blood flow, renal blood flow, glomerular filtration rate, and abdominal wall compliance.

The factors causing this problem could be spontaneous with peritonitis, a ruptured abdominal aneurysm [3, 19], intestinal obstruction, etc. Postoperative changes could be peritonitis, an abscess, acute gastric dilatation [28], or intraperitoneal hemorrhage [18]. After trauma, visceral edema could also be a factor and, of course, there are iatrogenic problems such as abdominal packing, reduction of massive hernias, etc. [29]. There are chronic causes such as large abdominal tumors, ascites, etc. [30].

In order to recognize and treat the abdominal compartment syndrome in anyone with abdominal distension, the bladder pressure should be measured [31]. Clinical observation may not be sufficient [32]. The answer, of course, with increased pressure to 25 mmHg, is to take the patient back to the operating room to operate or reoperate, open the abdomen and decompress it [33]. If the cause is due to blood or fluid, and this can be corrected, then it may be possible to close the abdomen. Frequently, however, it will be necessary to use some technique to leave the abdomen open for a brief time until the problem within the peritoneal cavity is corrected. Various materials have been used for this purpose. Marlex or PTFE is very expensive. Polypropylene sticks to the bowel and is no longer used. Knitted Dexon will last only for three weeks. The best material now seems to be polyglycolic acid. Woven vicryl mesh stays longer and seems to be quite satisfactory. If the skin can be closed over the top of the mesh, even though the fascia cannot be closed, this will help resolution of the intraabdominal process. Undermining of the skin in order to help close the skin or to close it either with towel clips or with some other form of closure can be helpful in allowing the process to resolve more quickly. As the pressure decreases, as the bowel edema subsides and other factors lessen, staged reconstruction of the abdominal wall may be necessary. It could be done in one stage if everything resolves quickly. Otherwise, it may take several stages.

A silastic membrane has also been used by many. The large wound is covered with a saline-soaked gauze dressing that is changed several times daily to

maintain the viability of exposed intraabdominal wall, subcutaneous tissue and fascia. The impermeable nature of this silastic, however, may be a drawback in not allowing drainage of fluid and other things, particularly if they are contaminated. There are many differences of opinion about materials and methods to be used [34-37]. The important principle is to recognize the syndrome before irreversible organ damage occurs.

Trauma and coagulopathy - The staged or abbreviated laparotomy

Severe abdominal and thoracic trauma may produce major organ injury to the liver, the spleen, the gut and the lungs, with massive blood loss and difficulty in controlling the situation operatively. This concept began with hepatic injury and the necessity to pack major liver injuries to control blood loss. For a time this was condemned; however, it became necessary to do so in order to save patients' lives. One of the first definitive approaches for this was by Feliciano et al., from the Ben Taub Hospital in Houston, Texas [38]. Patients with extensive liver injuries survived by packing the injury and returning the patient to the operating room after things were under better control. Shortly thereafter Svoboda et al., presented compelling information and experiences on severe liver trauma in the face of coagulopathy and made the case for temporary packing and early reexploration [39]. Since then there have been numerous reports of this approach. It has been called damage control [40], abbreviated laparotomy [41], planned reoperation [42], and of course staged laparotomy which seems to be the best term. Burch et al. [41] reported on 200 trauma patients with abbreviated laparotomy in which 98 (49%) survived to undergo reoperation and 66 of the 98 (67%) survived to leave the hospital. The supposition is that all would have died without this approach. Hirshberg et al. [42] found a mortality rate of 58% in such patients. Moore recently reviewed these problems in great detail in the Thomas Orr Memorial Lecture to the Southwestern Surgical Congress [5]. In this presentation he and his group described what they called the "bloody vicious cycle" (Fig. 1). They described this problem with massive torso trauma frequently involving the liver and other abdominal or thoracic organs. Coagulopathy develops with bleeding from everywhere. The patients frequently have had massive rapid blood transfusions, evidence of persistent shock, progressive metabolic acidosis with a low pH and refractory core hypothermia. The major criteria for these phenomena as described by Moore are shown in Table 1. When these criteria are met, or the bloody vicious cycle occurs with continued hemorrhage from everywhere, it is best to try to back off, conclude the operation very quickly, remove the patient from the operating room to the intensive care unit where the patient can be warmed, the coagulation problem is corrected, and other things brought into control. Then, at an appropriate and a more elective time, the patient can be taken back to the operating room to do more definitive repairs. The primary objectives of this approach are to arrest bleeding and then al-

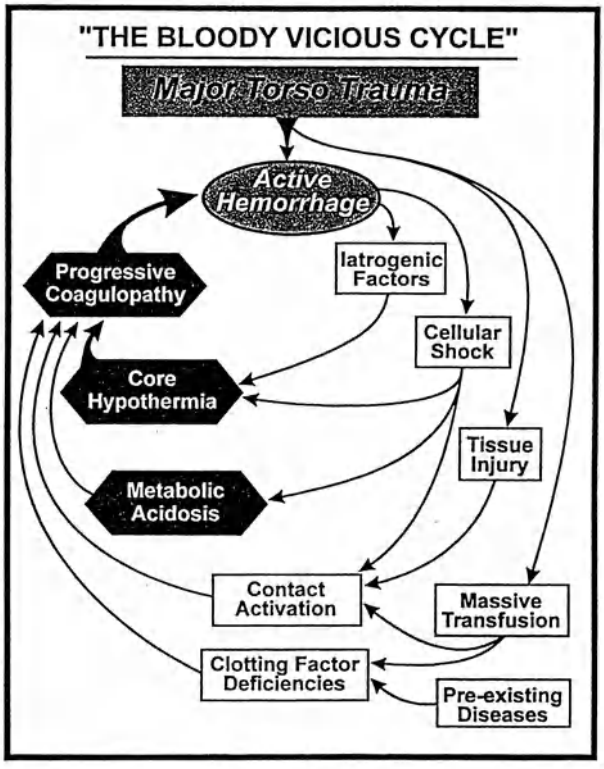

Fig. 1. The pathogenesis of the bloody vicious cycle following major torso injury is multifactorial, but usually manifests as a triad of refractory coagulopathy, progressive hypothermia, and persistent metabolic acidosis. (Reproduced with permission from [5])

Table 1. Major torso trauma

Coagulopathy - bleeding from everywhere
PT > 2 x normal
PTT > 2 x normal
Massive Rapid Transfusion
> 10 units/4 hours
Persistent Cellular Shock
$\dot{V}O_2 < 110$ ml/min/M^2
Lactate > 5 mmol/L
Progressive metabolic acidosis
pH < 7.20
Base deficit > 14 mEq/L
Refractory Core Hypothermia
< 34°C

low correction of the inciting coagulopathy. Emergency arrest of bleeding should consist of ligation, clamps which can be left in, intravascular balloons for hepatic vein or caval injury, tamponade by packing and other means. Contamination should be limited by excluding bowel injuries; there is no need to do primary anastomoses at this time. Finally, it is necessary to enclose the abdominal contents to protect the viscera. This can be done with plastic sheeting, using towel clips to bring the skin over the top of this. Usually the skin will be loose enough to do this and not produce an abdominal compartment syndrome. Physiologic restoration in the intensive care unit then consists of trying to increase the oxygen delivery index, using inotropes and cardiovascular support, if needed. Rewarming the patient is critical until the core temperature is above 35°C [43]. Blood components are given to raise the prothrombin time and the partial thromboplastin time back toward normal with a platelet count above 100,000 and a fibrinogen above 100 mm %. Mechanical ventilation is continued during this time.

Careful observation for potential development of the abdominal compartment syndrome is important. Timing of return to the operating room for the next stage of reexploration depends upon the response of the patient. Angiography with selective embolization may be necessary for major liver or other organ injury or pelvic fractures. Usually patients are returned to the operating room within 24 hours to complete cleaning of the peritoneal cavity, restoring bowel continuity and other matters. If there is extensive bowel edema, then reexploration may be delayed for 48 to 72 hours until such edema subsides to some extent. After cleaning the peritoneal cavity, abdominal wall reconstruction will have to be carried out and usually this will require a synthetic mesh template. The Moores in Denver have encountered enteric fistulae with absorbable polygalactin and polyglycolic acid as well as polypropylene and nylon mesh when they have been put over an exposed bowel. Polytetrafluoroethylene (PTFE) avoids fistulae because it does not adhere but it is terribly expensive, as mentioned early. Latex rubber and silastic are all alternatives but, of course, they require removal. Moore recommends individualizing trying to cover the gut with omentum if possible, then an absorbable mesh which can be sutured to the fascia [5]. If there is inadequate omentum, then latex rubber is placed over the exposed gut as the skin is gradually approximated. The ingenuity of the surgeon may be tested in carrying out such reconstructions. Although the mortality remains high (50%) with this approach, it is likely that the mortality would be 100% if the surgeon persisted in the operating room with the original operation.

Peritonitis and planned reoperation

The experts in the treatment of peritonitis now divide the problem into three types of abnormalities. First, there is primary peritonitis in which bacteria gain access to the peritoneal cavity either through lymphatics or via a blood-borne

mechanism. This occurs very rarely now and is primarily a disease of patients with cirrhosis and ascites which becomes infected. Patients undergoing peritoneal dialysis also may have primary peritonitis. Secondary peritonitis is defined as an infection occurring secondary to a disease process within the peritoneal cavity such as diverticulitis, appendicitis, perforated ulcer, etc. Tertiary peritonitis represents a failure of the initial treatment for secondary peritonitis with bacteria forming a chronic infectious state of multiple abscesses and other problems.

The following discussion will deal primarily with secondary peritonitis which has become generalized, rather than localized, and which is not amenable to drainage of the peritoneal cavity. This may be considered a form of tertiary peritonitis as well or may be considered to lead to tertiary peritonitis.

History of the development of treatment of peritonitis

For acute generalized suppurative peritonitis the results have never been totally satisfactory. Therefore, surgeons have sought better ways to improve the results and get more patients to survive. In the 1970's continuous peritoneal lavage was tried through catheters inserted within the peritoneal cavity for fluid administration and drains to remove it. It was then recognized that this was not very worthwhile [44]. Some continued the practice, however, of continuous flow irrigation [45]. In 1975 Hudspeth popularized the concept of radical peritoneal debridement, an extensive operation removing material on the bowel wall, on the mesentery, and so forth, debriding all the necrotic and/or inflammatory membranes and tissue [46]. Polk et al. in 1980 showed in a randomized trial that this was not worthwhile either [47]. In 1979 the concept of leaving the abdomen open was described by a number of French surgeons. One of the early reports in the English literature was by Steinberg entitled "On leaving the peritoneal cavity open in acute generalized suppurative peritonitis" [48]. This approach has been used in recent years in a number of different ways using packing, mesh, plastic materials, skin closure with towel clips and other approaches. Along with that, the concept of relaparotomy or another laparotomy on demand, when the clinical circumstances demanded it, was also considered.

Pichlmayr et al. in 1983 developed the concept of dorsal ventral lavage with a pallisade type of effect [49]. This concept has been pursued further by Losanoff et al., in which the pallisade of dorsal ventral lavage is applied after completing abdominal exploration and eradicating all septic foci [50]. A screen is fashioned from six to ten wide-bore silicone drains transfixed with stainless wire which keeps them together. The intestines are covered in this modification of Pichlmayr's technique by a large polyethylene foil with multiple perforations. It is placed far under the fascial edges. The screen is positioned over the polyethylene foil and secured in place with retention sutures to avoid evisceration. The abdomen is thus left open with a screen and underlying polyethylene

foil covering the viscera. Wide-bore inflow drains enter the abdomen dependently and laterally and three or four small-bore drains enter the space between the screen and the foil and then the laparostomy is closed with gauze. These drains are then used for continuous irrigation. This is a complicated technique which was modified from the original Pichlmayr technique which had led to the development of intestinal fistulae. The authors believe that this approach is satisfactory.

Planned relaparotomy was promulgated in 1986 by Teichman et al., with a technique of ettappenlavage, leaving the abdomen open with planned daily relaparotomy and irrigation [51]. More recently, the staged abdominal repair or STAR approach has been popularized. In a recent review of leaving the abdomen open Wittmann identified and used a new term called "open abdominostomy" in which there is no reapproximation of the abdominal fascia or wall. A second method is a mesh abdominostomy in which the open abdomen is covered with mesh [52]. One such technique is an improved zipper closure of the abdominal wall called the Ethi-Zip. The third approach, described in detail by Wittmann, is the STAR abdominostomy in which multiple planned laparotomies with staged reapproximation and final suture closure of the abdominal fascia is carried out utilizing a mesh with a zipper or suture, or other such approaches. The problems with these approaches are that they are used in terribly sick patients and it is difficult to know whether survival is improved by it or not.

Wittmann et al. have provided for us the management principles of peritonitis which included supportive measures and then operative treatment [52]. Principle 1: Repair by control of the source of infection, if this can be done. Principle 2: Evacuation of bacterial purulence and thorough irrigation. If the septic process has been controlled and the peritoneal cavity is clean, then that is all that is necessary to be done and many patients will do very well following this. Principle 3: With severe suppurative generalized peritonitis, there may be a need to decompress and treat the potential abdominal compartment syndrome. Principle 4: Control is to prevent or treat persistent and recurrent infection in which other procedures are necessary. Wittmann believes that the indications for a staged abdominal repair are: 1) a patient in critical condition with hemodynamic, ventilatory instability, 2) excessive peritoneal edema with swelling of the bowel which could lead to an abdominal compartment syndrome, 3) massive abdominal wall loss due to infection or gangrene, 4) impossibility to eliminate or control the source of infection, 5) incomplete debridement of necrotic tissue, 6) uncertain viability of remaining bowel, and 7) uncontrolled bleeding and the need for packing.

Wittman and Wallace reviewed 60 publications with a total of 1983 patients with peritonitis who met their study criteria [52]. They classified them into three approaches: an open abdominostomy (OPA), with a mortality of 42%, a covered/mesh abdominostomy, with a mortality of 39%, and a staged abdominal repair abdominostomy (STAR), with a mortality of 28%. Thus, the results tend to be better with the STAR approach. The complications of OPA are hernias [5]

and a large number of fistulae. With the second approach (covered mesh) hernias were frequent but fistulae were less frequent. With the STAR approach, hernias were infrequent as were fistulae. Thus, they believe that this is a best approach to go when it is necessary to do this.

Hau et al., in a case control study by the peritonitis group of the Surgical Infection Society of Europe, found that there was no significant difference in mortality between patients treated with planned relaparotomy versus relaparotomy on demand [53]. Postoperative multiple organ failure, as defined by the Goris score was more frequent in patients undergoing planned relaparotomy. Thus, the evidence for a major benefit from planned relaparotomy was lacking. A recent nonrandomized series failed to demonstrate the benefits of planned relaparotomies [54]. The complications were high [55]. However, another prospective study showed the staged abdominal repair approach to be superior to conventional operative therapy when the patient's mortality risks were compared by prognostic factors [56]. A 24-hour interval was recommended for the relaparotomy and reexploration and irrigation of the peritoneal cavity.

In 1993 Pusajó, along with Bumaschny et al., found that the use of an abdominal reoperation predictive index for peritonitis patients, as compared with just clinical judgment, was most useful in reducing mortality, the time elapsing between the first operation and relaparotomy, and the length of stay in the intensive care unit [57]. The abdominal reoperation predictive score was made up of whether or not the procedure was an emergency operation, whether or not there was respiratory failure, renal failure, ileus from 72 hours after operation, abdominal pain from 48 hours after operation, wound infection, consciousness alterations and symptoms appearing from the fourth day of operation. These are in essence the same variables that would be included in documenting the progressive development of organ dysfunction and potential multiple organ failure.

We are left with a dilemma. Is a planned relaparotomy and abdominal repair a futile procedure? Is it necessary? Is it helpful? When is it necessary? It is very difficult to randomize and come to a clear answer. What techniques are best? Some advocate a zipper technique [58]. Others strongly advocate a burr-like device [59]. It seems to me that there are patients who benefit from the planned relaparotomy with an open abdomen and intermittent irrigation and cleaning out the peritoneal cavity and there are those who are jeopardized by that approach. Andrus et al. also found the same mortality (38%) in patients treated by planned reoperation and those treated by expectant therapy – reoperation only if necessary [60]. Kinney and Polk provided an argument against the open treatment of peritonitis [61]. Now Wickel et al. have provided evidence that secondary peritoneal infection frequently resolved 77/105 patients with recurrent intra-abdominal infection in only 15 other patients [62]. Thus, disease acuity and organ failure were the causes of mortality. Thus, the disease process may be changing. Thus, there is no final answer. We must strive to do what is best for each individual patient to be sure that we are doing what seems like the logical best ap-

proach for them at that time. This alone will allow good judgment and better patient survival.

Conclusion

I have described two indications for operation and/or reoperation which are: 1) deterioration of remote organ function which may be due to an intra-abdominal focus; 2) treatment of the abdominal compartment syndrome. There are two reasons to stop operation and plan a reoperation: 1) the abdominal injury-hemorrhage, transfusion, hypothermia coagulopathy acidosis cycle; 2) the general suppurative peritonitis problem with planned reoperation and an open abdomen.

All of these approaches may be necessary and/or worthwhile in certain patients. Our job is to further learn when each should be used and how it is best used. The risks for the patients with these problems are high but the alternatives without these daring procedures are worse.

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Multiple Therapeutic Agents - Are We Making Progress?

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Immunotherapy in sepsis
is the Bermuda Triangle
of the Biotech Industry.

Phillip Dellinger, M.D.
Lecture to the Shock Society,
June 1997

It is not unusual to develop therapeutic agents in animal models which seem protective or therapeutic in the experimental animal but never proven to be worthwhile in patients. Over the years we have studied many such promising agents which never made a difference clinically. These include low molecular weight dextran, which is an anti-sludging agent, Dibenzyline (phenoxybenzamine), an alpha adrenergic blocking agent to decrease the intense vasoconstriction of shock, 2-3 diphosphoglycerate, which helps red cells unload oxygen in the peripheral circulation, polarizing solutions with homeopathic doses of Mg, K, insulin, glucose, and steroids, white blood cells which led to excess Ringer's lactate solution being given, buffers for extra-cellular acidosis, THAM tris(hydroxymethyl)amino-methane, an intracellular buffering agent, excess lactate and the L/P ratio, which would indicate anaerobiosis and steroids for septic shock [1-3]. In spite of many positive effects in the experimental laboratory, none of these substances ever came into clinical use for very long. When they were subjected to randomized clinical trials, they failed to improve survival or help patients. Recently, studies of injury, infection and inflammation have shown many mediators or agents which contribute to illness from such insults. This led to the development of agents which could block the harmful effects of such mediators. Many of these agents demonstrated excellent results in experimental animals and suggested great promise for clinical use. However, so far none of these agents (Table 1), when used individually, has had a positive effect in decreasing mortality in prospective randomized placebo-controlled trials in sick patients.

There are many reasons why such trials have been negative (Table 2) [4]. One important reason is that injury, infection and inflammation bring out complex changes and responses in the host. There are multiple pro-inflammatory mediators with overlap, redundancy and cross-stimulation. This is followed by

Table 1. Previous clinical trials of agents to control infection or inflammation

No improvement in 28-day mortality with	
HA-1A MAb to endotoxin	Pentoxifylline
J-5 MAb to endotoxin	Polyglobin
Tauralidine	Ibuprofen
IL-1 ra	PAF antagonists
Hydrocortisone in hyperdynamic septic shock	Bradykinin antagonist
Anti-TNF MAb	Anti-thrombin III concentrate
sTNFr	Interferon-gamma

Table 2. Problems with magic bullets

"Attempts to control the proinflammatory response were too crude"
Results would have been better if
– we had intervened at the proper time
– we had not overlooked the antiinflammatory response
– we had restored homeostasis through compensatory antiinflammatory response syndrome (CARS)
– we had had a mediator profile
– we had had a rapid endotoxin assay
– we had had a rapid culture technique
– we had known where the patient was in the inflammatory cascade process
– we had only entered patients at a high risk of dying
– we had been able to resolve the paradoxes and conundrums of many biologic activities (such as CD 11/18 MAb protects the lungs but worsens survival)
– sepsis had not been so heterogeneous
– we had known what we were doing
– we had treated diseases, not intellectual constructs
– the agents had been effective
– we had known that IL-6 was above 1000 picogram or LBP was high or whatever
– we had been able to recognize the heterogeneity in cytokine activities in patients with sepsis
– patient selection had been more appropriate
– we had been able to restore monocyte function before infection developed
– the end-point had not been 28-day mortality
– the end-point had been the reduction of the MODS score

an anti-inflammatory response to try to control the process before it gets out of hand. The timing and variability of these processes are inconsistent [5, 6]. Even with similar diseases there is great variability. This has led to consideration of multiple therapeutic agents for patients with diseases or injuries which stimulate an inflammatory response.

Multiple therapeutic agents in other diseases

There are many human diseases in which multiple agents are required for appropriate therapy. This includes antituberculous therapy for tuberculosis, immunosuppression for transplanted organs, ionotropes and diuretics for heart failure,

multiple antibiotics for polymicrobial peritonitis, cancer chemotherapy and support of the gastrointestinal tract. A review of several of these disease processes will illustrate the difficulties and the evolution that occurred in therapy with the addition of multiple agents.

The development of chemotherapy for tuberculosis and its evolution over the years will serve as an example of the problems even when dealing with a specific disease process and one organism which may be typical, atypical or may develop resistance to antibiotics. In 1944 Dr. Selman Waksman and colleagues isolated streptomycin [7]. It was found to be effective against tuberculosis in a small trial in 1945 [8], and this was followed by a large national trial in 1947, demonstrating impressive clinical results [9]. It was immediately apparent that there was a high incidence of relapse and the development of resistant organisms [10]. To counteract this effect, an agent p-aminosalicylicacid (PAS), a drug which had mild tuberculostatic activity, was used in combination with streptomycin in a trial in 1948-49 [11]. PAS extended the time during which streptomycin could be administered without developing resistance. In 1950 a specific program by industry led to the development of an antituberculous agent which was synthesized called isonicotinic acid hydrazide (INH) or isoniazid. This was found to be very effective in vitro and was strikingly successful in patients in 1952 [12]. This ushered in the modern era of chemotherapy. Other drugs were then developed. Presently recommended basic treatment for previously untreated patients with pulmonary tuberculosis in an initial phase are isoniazid, rifampin, and pyrazinamide given daily for two months followed by four months of isoniazid and rifampin [13, 14]. Ethambutol can be added in the initial two months if there is any suspicion of resistance or if the patient is thought to be HIV infected. Thus, there has been a steady and continuing evolution of appropriate multiagent chemotherapy for tuberculosis. We are reminded, however, that tuberculosis is a single disease even though there are variations in the organism, typical, atypical and resistant, etc., which primarily involve the lungs initially. Much of the development of successful treatment of tuberculosis was done by in vitro studies of the organism in culture and then trial and error clinically [15]. Also, each of the agents used in combination was effective for some time when used singly.

The development of cancer chemotherapy is another example of the complexities and difficulty in treating the manifestations and causes of human disease. Cancer chemotherapy was initially modeled after the multi-agent treatment of tuberculosis. Paul Ehrlich is said to have coined the word "chemotherapy" at the turn of the century. He used rodent models of infectious diseases to develop antibiotics. This led Clowes at Roswell Park Memorial Institute in the early 1900s to develop inbred rodent lines to carry transplanted tumors to screen for potential anticancer drugs [16].

The first modern chemotherapeutic agents were a product of a secret war gas program in both world wars. There was an explosion in Bari Harbor during World War II. Seamen were exposed to mustard gas which caused bone marrow and lymphoid suppression [17]. This led to trials in patients with hematopoietic

neoplasms such as Hodgkin's disease and lymphocytic lymphomas. This was first attempted at the Yale Cancer Center in 1943. Because of the secret nature of the wartime gas program, these results were not published until 1946 [18]. Initially, there was great excitement because of regression of these neoplasms but this was followed by discouragement because the tumors always grew back. This was followed by Farber's observation that folic acid accelerated leukemia and folic acid antagonists were developed [19]. Early therapy for childhood leukemias and Hodgkin's disease was with combination chemotherapy. There was then a long period of trial and error, observation of chemotherapy failure, and many other problems. DeVita states that, with some exceptions (choriocarcinoma and Burkitts lymphoma) single drugs and standard doses do not cure cancer [20]. In the early years of chemotherapy, drug combinations were developed based upon known biochemical actions of available anticancer drugs rather than on their clinical effectiveness. These were largely ineffective. DeVita states that the era of effective combination chemotherapy began when an array of active drugs from different classes became available for use in combination in the treatment of leukemias and lymphomas [21]. He concludes that, for multiagent cancer chemotherapy, only drugs known to be partially effective against the same tumor when used alone should be selected for use in combination. The least toxic drug should be used and given in an optimal dose and schedule. The principle of cancer chemotherapy has been clinical trial designed and dominated by the use of alternating cycles of combination chemotherapy [19]. Of course, the response to chemotherapy is affected by the biology of tumor growth. Thus, all cancers are different. They respond to very different agents. What is effective for one malignancy may do nothing for another. Malignancy is not a common denominator for therapy. Some tumors are hormone dependent, some respond to radiation therapy, some respond to chemotherapy and various combinations, some respond to both, some respond to operation with or without adjuvants. Staging and grade also have a lot to do with this. It is apparent also now that cure of malignancy is unusual and the malignant setting in patients is very important in terms of oncogene influence and genetic mutations and other factors.

Thus, the lessons learned from the treatment of tuberculosis and cancer indicate that specific diseases must be treated by a combination of agents, each of which has been shown to be individually effective in some way, shape or form. In addition, these processes of infection and neoplasia are chronic processes, they are not immediate, acute and life-threatening problems. Treatment can be carried out over many weeks. Thus, there are many dissimilarities between the use of multiple chemotherapy for these diseases and the possibility of using agents for the control of acute inflammation and of SIRS, MODS, and MOF.

Experimental studies of multiple agents for inflammation

Therapy for excess inflammation could require control or replenishment of a number of agents shown in Table 3. Several years ago one of us (H. Redl), along with G. Schlag, hosted a shock conference in Vienna during which a number of

Table 3.

Therapy for excess inflammation may require control of:	
Endotoxin	Coagulation activation
Pro-inflammatory cytokines	Adhesion molecule activation
Bradykinin	Complement activation
Proteinases	Cyclo- and lipo-oxygenase activation
Oxygen radicals	Histamine stimulation
Therapy may also require replenishment of:	
Antiinflammatory mediators	
Antioxidants	
Immunostimulators	

speakers presented models for the use of multiple agents or multiple component therapy for the treatment of sepsis and septic shock in critically ill surgical patients (May 7-11, 1995). Aasen and colleagues from Oslo, Norway, gave a presentation based upon a study in a pig model receiving endotoxin. They used a combination of three protease inhibitors (C1 inhibitor, antithrombin III and aprotinin) together with methylprednisolone, naloxone, ketanserin, and promethazine, which was found to counteract endotoxin-induced hyperdynamic changes [22]. This protected the animal against endotoxin-induced changes in the plasma enzyme cascade systems. At the same meeting Opal and colleagues from Brown University used an established infection model of *pseudomonas* sepsis and treated the animals with a combination of J-5 antisera, opsonophagocytic MAb, and anti-TNF MAb [23]. They found that this provided significantly greater protection than the single component therapy.

Faist presented a hypothesis for a combined therapeutic strategy which included 1) a global short-term (< 72 hours) downregulation of inflammatory monocyte activity via drugs like pentoxyfylline and IL-10 or IL-13, 2) the prevention of excessive monocyte stimulation by neutralization of circulating endotoxins with high-dose polyvalent immunoglobulins, BPI-bacterial permeability increasing protein, and soluble complement receptors, and 3) the cell mediated specific immune performance should be upregulated to overcome post-traumatic paralysis by administration of substances like thymomimetic hormones, gamma interferon, and granulocyte-colony stimulating factor [24]. At that conference Charles Fischer suggested that a combination of agents could be helpful and should be evaluated [25]. He listed BPIP for anti-endotoxin effects, IL-1Rra for anticytokine effects, antithrombin III to protect against the coagulation cascade, and a complement inhibitor to decrease the complement cascade.

There have been recent studies which change some of these hypotheses and proposals. For example, Mannick et al. found that a monoclonal antibody to IL-10 restored resistance to a septic challenge in an animal model [26]. Dalton et al. found that combined administration of interleukin-1 receptor antagonist (IL-1ra) and soluble tumor necrosis factor receptor (sTNF-r) decreased mortality and organ dysfunction in animals after hemorrhagic shock [27].

Demling et al., in Boston, used a combined chemotherapeutic regime in burn patients [28]. They gave antioxidants which include vitamins C, E and glutamine, with an endotoxin binder (parenteral polymyxin ß), a cyclo and lipoxygenase inhibitor, ibuprofen, and reconstituted human growth hormone. They believe that this improves mortality but it is based on historical controls.

Civetta and Kirton and colleagues in Miami used a multiagent approach for patients after trauma [29]. Kilbourn, Szabo, and Traber suggest that a combination of approaches that treat vasodilatation, multiorgan damage, metabolic dysfunction and coagulation abnormalities may be needed to treat septic shock [30]. They believe that there is still something worthwhile about nitric oxide synthase inhibitors in circulatory shock, like it was shown in recent nonhuman primates [31].

Ideal combinations of agents

Because of the many mediators, each of which seems to have a role in the pathogenesis of excessive inflammation, it makes scientific sense to use multiple agents. If we tried to put together an ideal combination of agents for excess inflammation, what would be the components? Certainly early on in the disease process some attempts to block pro-inflammatory mediators (Table 4) should be

Table 4.

Scavenging of inducers
Endotoxin - $rBPI_{21}$
Pro-inflammatory mediator blockade
1L-1ra
sTNFr
anti-TNF Mab - to restore function
Supplementation of anti-inflammatory agents
IL-10 - to reduce inflammation
IL-12, IL-13
Anti IL-10 Mab - to restore immune function
rHDL
Antioxidants
Protease inhibitors
Tissue factor pathway inhibitor
Cascade control
Coagulation - ATIII
Complement inhibitor
Cyclo- and lipo-oxygenase inhibition - ibuprofen
Histamine antagonist
Bradykinin antagonist
Control of other factors
PAF antagonist
Immunomodulators - drugs, diet
Anti-adhesion agents

worthwhile. Soon thereafter, supplemental antiinflammatory mediators would seem necessary.

Included should be control of the many enzyme cascades which are activated by shock, trauma or infection (Table 4). How many of these are necessary or important or possible is not known? How do we begin to formulate such an approach. What is the timing? What will be the cost? If the multi-agent cocktail becomes beneficial, what ingredients are critical, some may be ineffective. What is the model on which to test such approaches? One model is the sheep model developed by Regel et al. [32]. These models were reviewed by Redl et al. [33]. A baboon model which is in the final development stage could be helpful for multi-agent testing [31]. Would that fill the bill? Perhaps so, or do we also need new "multiple models" to cope with a "two or multiple hit" theory as suggested [34, 35]. In any case, it will be difficult to prepare a sufficient multidimensional protocol for such a study. We are told that the Food and Drug Administration in the United States would probably not approve a multi-agent approach. Perhaps a trial in Europe would help. In the meanwhile, we may learn more from multiple agents in animal studies.

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NEUROMUSCULAR DYSFUNCTION

SIRS and Sepsis-Induced Neuromuscular Dysfunctions

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Sepsis [1] has been increasingly associated with a severe systemic response to infection, usually resulting in early death. However, sepsis may be evoked in the absence of infection (e.g. trauma and burns), thus the term "systemic inflammatory response syndrome" or SIRS [2] is now used. Considering the profound changes induced by SIRS, it is not surprising that the nervous system is affected (Fig. 1). The chief manifestations are septic encephalopathy and critical illness polyneuropathy, each occurring in approximately 70% of septic patients [3].

Investigating neuromuscular conditions in the Intensive Care Unit (ICU)

One should first exclude conditions which may not have SIRS as an underlying factor and begin before admission to the critical care unit. Acute infective, traumatic or neoplastic spinal cord compression, Guillain-Barré syndrome, myasthenia gravis, muscular dystrophy, and so forth, are usually obvious before endotracheal intubation and placement on a ventilator. However, occasionally, the conditions worsen so rapidly that an early diagnosis is not possible. These conditions must then be investigated while the patient is in the critical care unit. Then consider patients who have been admitted to a critical care unit for a variety of severe, primary illnesses or injury, develop SIRS, are observed to have difficulty in weaning from the ventilator and limb weakness. An underlying neuromuscular condition can be suspected if, after lung or cardiac causes of respiratory insufficiency have been eliminated, on attempted weaning, voluntary respirations are rapid and weak and accompanied by a rising blood CO_2. Neurological signs of neuropathy or myopathy may or may not be present. The main features of these conditions are summarized in Table 1.

Involvement of the high cervical spinal cord, peripheral nerves, neuromuscular junctions and muscles should be systematically investigated. It may be necessary to perform one or more of MRI scanning of the cervical spinal cord; motor and sensory nerve conduction; repetitive electromyography of muscle, tests of the respiratory system by phrenic nerve conduction studies and needle

Table 1. Neuromuscular conditions in the critical care unit associated with SIRS

Conditions	Incidence	Clinical features	Electro-myography	Creatine Phospho-kinase	Muscle biopsy
A. *Polyneuropathy*					
Critical illness polyneuropathy	Common	Flaccid limbs, and respiratory weakness	Axonal degeneration of motor and sensory fibres	Near normal	Denervation atrophy
Motor neuropathy	Common with neuromuscular blocking agents	Flaccid limbs, and respiratory weakness	Axonal degeneration of motor fibres	Near normal	Denervation atrophy
B. *Neuromuscular Transmission Defect*					
Transient neuromuscular blockade	Common with neuromuscular blocking agents	Flaccid limbs, and respiratory weakness	Abnormal repetitive nerve stimulation studies	Normal	Normal
C. *Myopathy*					
Thick filament myopathy	Common with steroids, neuromuscular blocking agents and asthma	Flaccid limbs, and respiratory weakness	Abnormal spontaneous activity	Elevated	Central loss of thick filaments
Disuse (cachectic myopathy)	Common (?)	Muscle wasting	Normal	Normal	Normal or type 2 fibre atrophy
Necrotizing myopathy of intensive care	Rare	Flaccid weakness, Myoglo-binuria	Abnormal spontaneous activity in muscle	Markedly elevated	Panfascicular muscle fibre necrosis

(With permission from [4])

electromyography of the diaphragm; measurements of serum creatine phospho-kinase; and biopsy of muscle [3-5, 6].

Critical illness polyneuropathy

After the development of SIRS the earliest nervous system manifestation is septic encephalopathy. Within hours of the appearance of a positive blood culture, careful testing may reveal impaired attention, concentration, orientation and writing [7]. If the SIRS continues, the patient gradually slips into deep coma,

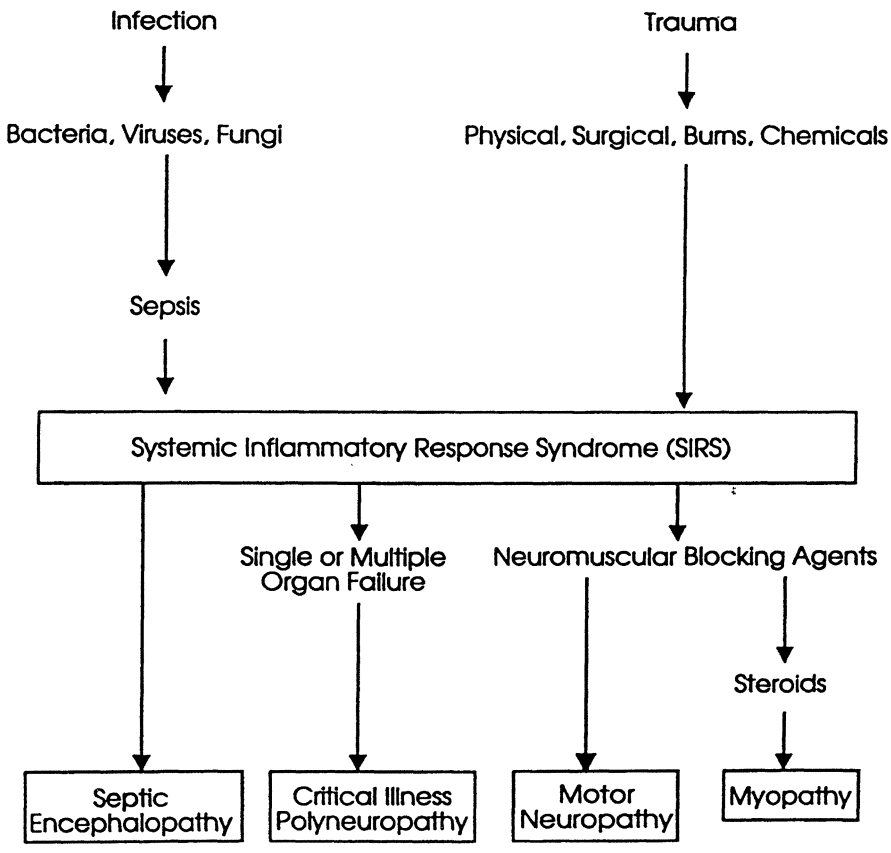

Fig. 1. The various factors associated with the development of the systemic inflammatory response syndrome (SIRS) and its nervous system complications. (Adapted with permission from [4])

usually without the development of focal signs, seizures, myoclonus or asterixis. The electroencephalogram (EEG) is a sensitive indicator of the presence and severity of septic encephalopathy. Head scans and cerebrospinal fluid examinations are usually unremarkable [8].

If SIRS can be treated by antibiotics, surgical drainage of an infected focus, inotropic drugs and fluid replacement, the encephalopathy usually improves rapidly but, at this time, it will be noticed that there is a difficulty in weaning from the ventilator. Studies in our unit indicate that the commonest neuromuscular cause for this, after cardiac and pulmonary causes have been excluded, is critical illness polyneuropathy [9-11]. However, clinical signs of neuropathy, including depressed deep tendon reflexes, are present in only half of these patients. Hence, electrophysiological studies are necessary to establish the diag-

nosis. A more severe polyneuropathy can, however, be suspected when, on deep painful stimulation of the distal extremities, it will be noted that limb movements seem clearly weak despite strong grimacing of facial musculature.

In the ICU, central respiratory drive may be assess by temporarily decreasing ventilatory support to 5 to 8 cm H_2O of pressure support or continuous positive airway pressure (to overcome airway/ventilator resistance), for a maximum of 15 minutes. Mechanical ventilation is restored if there is evidence of respiratory distress, arterial oxygen saturation < 90% (based on a pulse oximeter reading) or a significant rise in heart rate or blood pressure. We found it is advantageous to do this at the same time that we perform needle electromyography of the diaphragm. The presence and types of disorders of central drive can be more accurately assessed.

The earliest electrophysiological sign is a reduction of compound muscle action potential amplitudes, with minor change in latency. This is typical of axonal damage and occurs with one week. Fibrillation potentials and positive sharp waves may not appear in muscle until three weeks. Motor unit potentials, if they can be voluntarily activated by the patient (and may not be due to sedation or septic encephalopathy) will often appear normal or somewhat low amplitude and polyphasic, suggesting an associated primary involvement of muscle by sepsis. These electrophysiological changes could also be due to a primary myopathy. Hence, it is important to demonstrate depression of sensory compound action potential amplitudes before a firm electrophysiological diagnosis of polyneuropathy can be made. Repetitive nerve stimulation studies to demonstrate a defect in neuromuscular transmission should also be performed. We have shown that this does not occur in sepsis but will be present if neuromuscular blocking agents have been used. Their effects may persist beyond several hours, to a number of days if the patient is in renal or liver failure [12]. It is also important to do phrenic nerve conduction studies and needle electromyography of the chest wall and diaphragm, to establish that the difficulty in weaning from the ventilator is, in fact, due to critical illness polyneuropathy [6].

In CIP [9] there is a primary axonal degeneration of peripheral nerve motor and sensory fibers, but no evidence of inflammation, as may be seen in Guillain-Barré syndrome. Muscle shows scattered atrophic fibers in acute denervation, and grouped atrophy in chronic denervation. There are occasional necrotic muscle fibers, suggesting an associated primary myopathy. The only central nervous system manifestation is central chromatolysis of anterior horn cells and loss of dorsal root ganglion cells, secondary to the peripheral nerve axonal damage. No changes appear distinctive of critical illness polyneuropathy.

Knowledge of the presence of critical illness polyneuropathy aids management on the ventilator and, in particular, indicates that the patient has a neuromuscular problem, which may prolong care in the critical care unit. If it is a mild polyneuropathy, recovery is expected to occur within a matter of weeks, but if it is severe it may take months. In physiotherapy a rehabilitation tailored

to polyneuropathy should be instituted. Critical illness polyneuropathy is associated with increased mortality and rehabilitation problems [13]. A few instances of critical illness polyneuropathy in children are now being observed [14-16].

To date, there has been no specific treatment for CIP. An open trial of high dose intravenous immunoglobulins was not effective [17].

Other neuromuscular complications of SIRS

Acute motor neuropathy associated with competitive neuromuscular blocking agents

In this condition [18-24], the patient will have been in the ICU for several days, or possibly weeks, and competitive neuromuscular blocking agents, such as pancuronium bromide, or the shorter-acting vecuronium, will have been given to ease mechanical ventilation. These will have been used for longer than 48 hours, occasionally days or weeks. When these agents are discontinued, difficulty weaning from the ventilator and limb paralysis are noted. The serum creatine phosphokinase is mild or moderately elevated. Electrophysiological testing may or may not reveal a defect in neuromuscular transmission. If present, it will be demonstrated on slower rates of stimulation, to be expected in a post-synaptic defect. There is evidence of a severe, primary axonal degeneration, of predominantly motor fibers, on nerve conduction and needle electromyographic studies. Muscle biopsy shows varying degrees of denervation atrophy and muscle necrosis. I believe that SIRS is an important underlying factor in most, if not all, of these patients [25]. If the various systemic complications can be treated successfully, the neuromuscular condition, itself, improves spontaneously and good recovery may occur, sometimes quite rapidly. However, the neuromuscular blocking agent likely has an additional toxic effect on nerve and muscle, and its use should be avoided, if possible.

Transient neuromuscular blockage

Competitive neuromuscular blocking agents are metabolized or cleared by the liver and kidney. Hence, in the presence of failure of these organs, the effect of the neuromuscular blocking agent may be quite prolonged, for a number of days, after it has been discontinued [12]. Repetitive nerve stimulation will correctly identify the defect in neuromuscular transmission. However, by the time of testing, many of these patients will already have developed an underlying critical illness polyneuropathy, in addition to a neuromuscular transmission defect, each disclosed by electrophysiological studies. Here, recovery will not occur in a short period of time but may be prolonged for several weeks, or even months in severe cases.

Thick filament myopathy

A distinctive syndrome [13, 22, 26-28] occurs in children or adults in the setting of sudden, severe asthma or in the post-transplant state. Endotracheal intubation and placement on a ventilator is necessary. High dose steroids and neuromuscular blocking agents to ease ventilation are given, often for a number of days. Again, on attempted weaning from the ventilator, it will be noted that the patient has severe neuromuscular respiratory insufficiency and limb weakness. Ophthalmoplegia may be present [29]. Creatine kinase levels are often considerably elevated. Repetitive nerve stimulation studies are usually normal. Sensory conduction is normal, as is motor conduction, except for a low amplitude compound muscle action potential. On needle electromyography, motor unit potentials tend to be low amplitude, short duration and polyphasic, indicating a primary myopathy. Muscle biopsy shows a loss of structure centrally in muscle fibers. Under the electron microscope, this has been shown to be due to destruction of the thick myosin filaments [27]. Denervation of muscle, secondary to either critical illness polyneuropathy or the neuromuscular blocking agent, likely predisposes to this distinctive pathological change [25, 30]. Recovery occurs quite rapidly. The clinical and electrophysiological features are usually so distinctive in this syndrome that muscle biopsy is often not necessary, a worthwhile consideration in children because of the disfiguring scar. Thus, neuromuscular blocking agents should be used to ease ventilation only when there are clear-cut indications, and in as low a dosage and for as short a period as possible.

Cachectic myopathy

Cachectic myopathy, disuse atrophy and catabolic myopathy [31] are often cited as complications of critical illness. However, even though they cause muscle weakness and wasting, all are ill-defined in clinical terms [25]. Motor and sensory nerve conduction studies, needle electromyography of muscle and creatine kinase levels are all normal. Muscle biopsy may be normal or show Type 2 muscle fibre atrophy, a nonspecific finding.

Acute necrotizing myopathy of intensive care

It may be precipitated by a wide variety of infective, chemical, and other insults, basically involving the differential diagnosis of acute myoglobinuria [32]. It would be expected to occur with increased frequency in critical care units, in which there is a high incidence of trauma, infection and the use of various medications. There is severe weakness with high levels of CPK and often myoglobinuria. Electrophysiological studies were consistent with a severe myopathy, and muscle biopsy showed widespread necrosis of muscle fibers. Rapid and spontaneous recovery is expected to occur in milder cases, but in more severe cases the prognosis may be poor [32-35].

Recent studies on myopathy in critical illness have been quite interesting. Latronico et al. [36] observed on combined biopsy of superficial peroneal nerve and peroneal brevis muscle evidence of muscle pathology, and in only 8 was it clearly that of denervation atrophy. The nerve biopsy indicated an axonal neuropathy in 8 of 22 patients. However, these biopsies were performed very early in the course of the critical illness perhaps before structural changes had time to take place, and electrophysiological studies clearly pointed to an axonal motor and sensory polyneuropathy in most of these patients. Rich et al. [37] in Philadelphia developed and applied the technique of direct muscle stimulation to 14 critically ill patients. In eleven the amplitude ratio of nerve/muscle stimulation indicated a primary myopathy and in five a neuropathy.

Lacomis et al. [38], studied 14 critically ill patients prospectively. They were either post transplant, or being treated for severe pulmonary disorders and sepsis. They all received neuromuscular blocking agents and steroids. A severe necrotic myopathy resulted in 79% in which there was a selective loss of thick myosin filaments. Creatine phosphokinase values were normal or only mildly elevated. However, sensory conduction studies were abnormal in approximately 50%, indicating there was likely an associated critical illness polyneuropathy in a significant number of these patients. Recovery from the myopathy occurred within 3-4 months in patients who survived. However, in recent prospective studies by Berek et al. [39], and Leijten and De Weerd [40], there was no correlation with the use of these agents and neuromuscular disease. The results in the present study were similar. Thus, the precise role of NM blocking agents and steroids in causing a critical illness myopathy is still in doubt.

Pathophysiology

Retrospective [9] and prospective [41] studies have failed to incriminate a variety of potential causes of critical illness polyneuropathy, including types of primary illness or injury, Guillain-Barré syndrome, medications including amino glycoside antibiotics and neuromuscular blocking agents and specific nutritional deficiencies. We have speculated that sepsis is the cause [9, 41].

The micro circulation is disturbed in sepsis (Fig. 2). Blood vessels supplying peripheral nerve lack autoregulation [42]. Cytokines that are secreted in sepsis have histamine-like properties which may increase micro vascular permeability [9]. The resulting endoneurial edema could induce hypoxia. Severe energy deficits would result and induce a primary axonal degeneration, most likely distally, if highly energy-dependent systems involving axonal transport of structural proteins are involved. The predominantly distal involvement may explain why recovery in some patients may be surprisingly short, conforming to the short length of nerve through which axonal regeneration takes place.

Through increased capillary permeability induced by the sepsis, neuromuscular blocking agents, notably vecuronium or its metabolite, 3 desacetyl-vecuro-

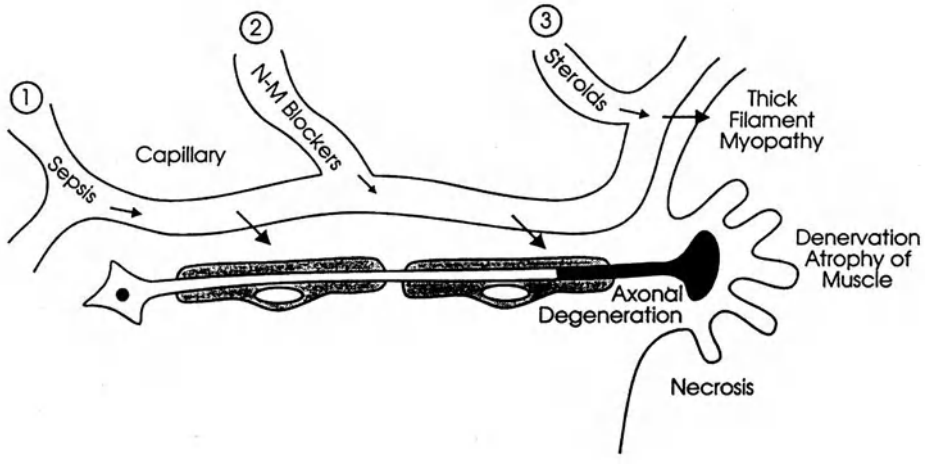

Fig. 2. Theoretical mechanisms of neuromuscular complications of SIRS. 1. Sepsis induces a release of cytokines which cause increased capillary permeability. This, and other microvascular mechanisms, induce a critical illness polyneuropathy, with distal axonal degeneration of nerve and denervation atrophy of muscle. 2. Neuromuscular (N-M) blocking agents in the presence of SIRS traverse the hyperpermeable capillary membrane and have a direct toxic effect on nerve, or cause "functional denervation" to increase denervation of muscle. 3. Steroids gain access to muscle by this mechanism and, in the presence of denervation due to 1 and 2, induce a thick filament myopathy and varying degrees of necrosis. Combinations of 1, 2, and 3 may occur in the same patient. (Adapted with permission from [3])

nium [12], could have a direct toxic effect on peripheral nerve axons. These neuromuscular blocking agents may also cause functional denervation through their prolonged neuromuscular blocking action [43]. Hund et al. [44] have identified in the serum of CIP patients a factor which is toxic to cultured neurons from fetal rat spinal cord.

In the acute myopathy which develops when patients are treated with neuromuscular blocking agents and steroids, we suspect infection is often a precipitating event. Animal experiments by Karpati et al. [30] have shown that if the muscle is first denervated by nerve transection and then steroids are given, a thick filament myopathy similar to that seen in humans can be induced. Thus, in the human condition, critical illness polyneuropathy and the additional effects of neuromuscular blocking agents would denervate muscle and then steroids would induce the typical myopathic changes. Corticosteroids may activate an ATP - ubiquitin dependent proteolytic system [45], or proteolysis may be initiated through calpain expression, which alters calcium homeostasis [46].

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PREVENTION AND MANAGEMENT OF SEPSIS AND MODS

Lights and Shadows in Sepsis and Multiple Organ Dysfunction Syndrome (MODS)

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In the last decade, understanding of the basic pathophysiologic mechanism underlying the development of sepsis and septic shock has made impressive progress. New discoveries have challenged previously accepted concepts of infection and sepsis, and profound revisions and new therapies have been proposed. This scientific revolution led to the implementation of several large clinical trials employing new agents aimed at preventing or blocking the release of mediators involved in the development of the systemic inflammatory response characteristic of sepsis and related disorders, ultimately leading to Multiple Organ Dysfunction Syndrome (MODS). Unfortunately, the overall results indicate that these novel approaches have not been associated with a substantially improved outcome of septic patients, and in many cases both the design and the results of these trials have been criticized [1].

On the basis of these considerations, it appears that the clinical fall-out of these discoveries lies far away from the expectations derived from the more in-depth understanding of the biology of sepsis, and that, in many cases, areas of bright light are interrupted by spots of deep shadow. In this chapter, we shall focus on some of the many controversial points existing in the area of sepsis and related consequences.

Lights and shadows on definitions

A 41-year old man was admitted to the hospital with acute abdomen and shock. The patient required artificial ventilation and cardiovascular pharmacological support. An explorative laparotomy revealed severe ischemia of the intestinal loops caused by thrombosis of the superior mesenteric artery. An extensive intestinal resection was performed. After the intervention, the patient's conditions remained unchanged, and were characterized by shock associated with coagulative abnormalities (fibrinogen = 50 mg/dl, platelets = 15.000/ml, PT = 18 secs, FDP > 70 mcgr/ml, ATIII < 40%). All cultures remained sterile, and blind therapy with antibiotics was instituted. Despite the aggressive hemodynamic and respiratory support and the repeated transfusions of fresh frozen plasma, the patient ultimately died. The autopsy revealed diffuse peritoneal inflammation and dif-

fuse microvascular thromboses associated with the hemorrhage of the adrenal glands.

The time-honored term septicemia almost disappeared from current medical literature when the critical care community realized that a more precise definition of certain clinical settings was urgently needed. Two main considerations led to the redefinition of these conditions. Firstly, just as patients enrolled in the clinical trials had to be comparable, also the diagnostic definitions had to be standardized. Indeed, although every experienced intensive care specialist is able to recognize, or define, a patient in septic shock, confusion could arise in the description of patients with less severe, infection-related systemic disorders. Secondly, both patients with severe infection and those following non-infective events (e.g. ruptured aortic aneurysms, acute pancreatitis, etc.) may share the very same symptoms of fever, leukocytosis and hypotension, since the same biological mechanisms are involved in the pathogenesis of the disturbances. As a consequence, it appeared useful to separate patients in whom an infection had triggered the systemic symptoms, from those in whom an infection was unlikely or, at least, not demonstrated. Thirdly, it might be useful, in a retrospective analysis, to identify some easily recognizable symptom(s) heralding a worsening of patients' conditions.

A number of leading authorities in the field of critical care then proposed a new classification system to be adopted in the diagnosis of patients with severe systemic disturbances [2]. According to these definitions, it thus became possible to identify the following clinical entities:

systemic inflammatory response syndrome (SIRS), which is characterized by two or more of the following conditions: temperature > 38°C or < 36°C, heart rate > 90 bpm, respiratory rate > 20 breaths/minute or $PaCO_2$ < 20 mmHg, leukocytosis (> 12.000 WBC/ml) or leukopenia (< 4.000 WBC/ml), in the absence of an infection. Acute pancreatitis or the postoperative state following the repair of a ruptured aortic aneurysm are typical clinical examples of SIRS, which is supposed to be caused by the production and release of a number of mediators activated by a non-infective stimulus;

sepsis, which includes the very same alterations described above for SIRS, but in the presence of an infective focus;

severe sepsis and septic shock, which are characterized by the occurrence of hypotension and signs of organ malfunction, requiring the infusion of large amount of fluids or the administration of vasoactive drugs.

multiple organ dysfunction syndrome (MODS), characterized by the simultaneous dysfunction of multiple organs. This definition offers a more accurate description of the situation previously indicated as multiple organ failure (MOF), because the passage from a normal functioning to a totally failing organ occurs along a continuum of ever-decreasing function and is not an "all-or-nothing" phenomenon. At the same time, the term "dysfunction" conceptually implies a certain degree of reversibility, which is almost totally lost in the term "failure".

For instance, in many critically ill patients a mild increase of azotemia and creatinemia is common, and their values return to the baseline with a more aggressive volume therapy and/or a judicious use of diuretics. In this particular situation, the diagnosis of acute renal failure would be inappropriate.

Since these definitions are a compromise deriving from different points of view, they have not been universally accepted [3, 4]. Heavily criticized is the unspecificity of the definition of SIRS in that it yields poor prognostic information, as its symptoms can be present in patients with disorders associated with an extremely different outcome. However, if the clinical evolution of patients in SIRS is taken into account, it appears that in many instances SIRS may be considered a precursor of sepsis, and a more comprehensive diagnostic approach should be implemented as soon as this condition is recognized [5]. Actually, in patients admitted to a surgical critical care unit, Pittet et al. [6] demonstrated that a) SIRS was almost universally present (93%) in the patients enrolled, and b) more than half (53%) of these patients subsequently developed sepsis. Furthermore, all patients who developed severe sepsis had previously been diagnosed to be in sepsis. The authors concluded that there was a progression from SIRS to sepsis and severe sepsis, even if the diagnostic criteria of SIRS were so wide that almost every patient fulfilled them, and thus that the definition of SIRS was sensitive but not specific. The same group demonstrated that this progression was also present in a larger group of medical, surgical and respiratory patients, and that there was an inverse correlation between the number of criteria used to diagnose SIRS and the time interval (in days) between the diagnosis of SIRS and the onset of sepsis [7]. In patients enrolled in a large Italian multicenter study, also Salvo et al. [8] observed that prognosis was progressively worse in patients diagnosed to be in sepsis, severe sepsis and septic shock; however, these authors failed to demonstrate any prognostic difference between patients in SIRS and those who did not fulfill its diagnostic criteria, concluding that SIRS yields little or no diagnostic and/or prognostic information.

Lights and shadows on anti-mediator agents

A 58-year old man was admitted to the ICU due to a peritonitis-associated septic shock which occurred 5 days after a right hemicolectomy for cancer. The patient was operated again, a purulent collection was drained, and antibiotic treatment was instituted. Despite this approach, the hemodynamic and respiratory conditions further deteriorated, requiring continuous infusion of norepinephrine and dobutamine at ever-increasing dosages. As the entry criteria had been fulfilled, the patient was enrolled in a double-blind, placebo-controlled, multicentre trial of anti-TNF antibodies. Despite an aggressive treatment which included repeated percutaneous drainages of abdominal collections, the clinical conditions worsened and, 30 days after the enrolment in the trial, the attending physicians and the family agreed to discontinue the treatment, whereupon the patient

died a few hours later. The pharmaceutical company responsible for the trial recorded him as a survivor.

The wide array of cardiorespiratory and metabolic derangements commonly observed in sepsis is caused by the production and the release, by immunocompetent and endothelial cells, of a number of mediators resulting from the interaction between the infecting agent and the host [9, 10], including the tumour necrosis factor (TNF), the platelet activating factor (PAF), an ever-increasing number of Interleukins (IL), the endothelin, arachidonic acid derivatives, and many others. The same substances are also implicated in the development of SIRS [11]. As in other biological systems (e.g. the coagulative cascade), the secretion of many, if not all of these mediators is accompanied by the simultaneous release of substances with inhibitory properties, teleologically aimed at down-regulating the inflammatory process [12]. Basically, these agents act by binding and inactivating the circulating septic mediators or by occupying their receptors on the surface of the target cells, thus making them unavailable for the active mediators [12].

Since the late 1980s, greater in-depth knowledge of the basic pathophysiologic mechanisms underlying the septic process, and the impressive progress of genetic engineering techniques have led to the development of many substances able to blunt the effects of the septic mediators. This goal can be accomplished in different ways [13]. First, circulating endotoxin and septic mediators can be inactivated by specific antibodies. Secondly, cell receptors can be selectively blocked by specific antagonists. Finally, bloodborne mediators can be blocked by binding them to soluble receptors identical to those present on the cell surface. It is evident that, in many cases, these strategies reflect what is already occurring spontaneously in septic organisms. Unfortunately, despite the sound pathophysiologic basis and the promising experimental data, the overall results deriving from many large double-blind, placebo-controlled clinical trials using different anti-mediator strategies have so far been disappointing or far below the expectations, since some beneficial effects could only be demonstrated in certain subgroups of patients [1]. Moreover, some trials had to be suspended when an interim analysis demonstrated excess mortality in the treatment group [1].

A number of anti-endotoxin antibodies were the first agents to be studied. At the beginning of the 1980s, Ziegler et al. [14] showed that increased survival was associated with the administration of human polyclonal antibodies against the lipid A [15]. These results were confirmed by two other clinical studies which utilized polyclonal antiendotoxin sera [15, 16]. The major drawbacks of this treatment consisted in the instability of the solution, in the difficulty of measuring the real protective effect of a polyclonal preparation, and in the risk of transmissible diseases [17]. Thanks to the recent impressive development of genetic techniques, it was possible to overcome these disadvantages. As a result, ten years later, two large, multicenter, double-blind, placebo-controlled studies demonstrated a better outcome in septic patients who had been given antiendotoxin antibodies. The first trial involved 486 patients with suspected

Gram- sepsis who received E5, a murine monoclonal IgM anti lipid A antibody or placebo [19]. Although the overall mortality rate was comparable in the two groups, in the subset of patients with confirmed Gram- septic shock, mortality was slightly higher in the placebo group, whereas it was significantly lower in treated patients with sepsis but not in shock. During the same period, another trial was performed using human monoclonal IgM antiendotoxin antibodies (HA-1A) (given as a single bolus of 100 mg i.v.) [20]. Contrarily to what had been reported with E5, a better survival rate was observed in patients with confirmed Gram- bacteremia and septic shock. In non-bacteriemic, non-shocked patients with Gram- infection, mortality was higher in the treatment than in the placebo group. Subsequent data analysis demonstrated that HA-1A was particularly effective in patients with higher blood endotoxin levels [17]. In addition to these main studies, other investigators demonstrated that in a limited number of patients the administration of either E5 or HA-1A was well tolerated, that it was associated with reduced mortality and was not accompanied by major side effects [21, 22]. However, a more recent randomized, double-blind, placebo-controlled study with E5 failed to demonstrate any effect on survival, although it was associated with greater resolution of organ failure in the treated group [23]. After its publication, some doubts have been raised about the results of the HA-1A study [24]. The areas of major concern were the randomization and the concomitant treatment (the placebo group was older, had a higher APACHE II score and a higher rate of inadequate therapy with antibiotics). To test its effectiveness conclusively, another multicenter, double-blind study was started, using HA-1A. However, interim data analysis revealed slight and non-significant excess of mortality in non-bacteriemic patients given HA-1A, and the study was suspended.

Other clinical trials which involved anti-mediator agents shared the same destiny. As TNF is supposed to be released early in sepsis and exert multiple-systemic detrimental effects [9, 10], several investigations focussed on the possible therapeutic effects of its antagonism in septic patients. Experimentally, antibodies directed against TNF exert a protective cardiovascular effect in animal models of septic shock [25]. Early clinical experiences were encouraging, sometimes indicating a rise in arterial pressure [26] and an improvement in left ventricular function [27]. A preliminary clinical trial involving only 42 patients demonstrated that the administration of anti-TNF antibodies was free from harmful side effects and associated with a substantial decrease of circulating TNF molecules [28]. Unfortunately, two large, double-blind, placebo-controlled trials with different anti-TNF antibodies failed to demonstrate any effect on the mortality of septic patients [29, 30]. However, in one of these studies, when treated patients were retrospectively divided into subgroups, an improved outcome could be demonstrated in patients with elevated baseline plasma levels of IL-6 [30]. A confirmatory trial was then launched, in which only septic patients with plasma IL-6 levels > 1000 pg/ml were enrolled. The study was suspended by the regulatory authorities when an interim analysis demonstrated that the results were inconclusive.

As stated above, inactivation of septic mediators can also be accomplished in other ways, for instance by the administration of agents able to selectively block the receptors on the cell surface, making them unavailable for the active substance, or by the interaction with specific circulating receptors which bind the mediator and so prevent the contact with the target cell. IL-1ra has also been isolated in healthy volunteers given endotoxin [31]. So far, a number of trials have been performed using the receptor-blocking agent of IL-1 (IL-1ra), the soluble receptor of TNF and the PAF receptor antagonist. The potentially beneficial effects of these substances have been experimentally demonstrated in many experimental studies. Rabbits given E. coli intravenously and treated with IL-1ra show only a transient early hypotension, suggesting that TNF could be responsible for the early phase of septic shock, whereas IL-1 is implicated at a later stage [32]. Experimentally, the administration of IL1-ra has been associated with an improvement of cardiovascular function and a reduction of mortality [33-35]. On the basis of these encouraging results, some clinical trials of IL-1ra in septic patients have been implemented. A randomized, open-label multicenter Phase II study was performed in the United States. It involved 99 septic patients, who were given an initial loading dose of IL1-ra or placebo, followed by a 72-hours continuous infusion of one of three different doses [17, 67 or 133 mg/hr, respectively) or placebo [36]. The endpoint of the study was survival at 28 days. In the treatment group, a dose-related increase in survival was observed, mortality being 44% in the placebo group, 32% in patients receiving the lowest dosage, 25% in patients receiving the intermediate dosage, and 16% in patients receiving the highest dosage. At the end of the infusion, the severity of the disease, as expressed by the APACHE II score, was reduced in the treatment group. On the basis of these results, a larger, randomized, double-blind, placebo-controlled Phase III trial was launched. The trial involved 893 patient receiving either placebo or IL1-ra, which was administered as an intravenous loading dose of 100 mg followed by a 3-day infusion at two different dosages (1 or 2 mg/kg/hr, respectively) [37]. Unfortunately, the results of this study failed to confirm those of the previous one. Actually, no significant reduction in mortality was observed in the treated patients as compared with the controls (29% vs. 35%, respectively). Some secondary retrospective analyses demonstrated a better outcome in patients with dysfunction of one or more organs, and in patients with a predicted risk of mortality $\geq$ 24% [37, 38]. The results of these studies were so different that a second Phase III study was then performed, on the assumption that if the trend toward a better outcome could be demonstrated by a more sophisticated statistical analysis, then the IL1-ra could be clinically valuable, at least in selected subgroups of patients. However, this trial had to be suspended when an interim analysis demonstrated the futility of the results [1].

Other investigations focussed on the effects of the TNF soluble receptors. In septic organisms, the effects of TNF are mediated through 55-kd (TNFR I) and 75-kd (TNFR II) receptors, whose extracellular domain is shed from the cells during sepsis, and, once released into the interstitial space and in the blood-

stream, they bind the circulating TNF molecules, thus blocking their effects [39]. Experimentally, the administration of soluble TNF receptors is associated with the attenuation of the increased pulmonary permeability and the neutrophil sequestration induced by an intestinal ischemia-reperfusion injury [40]. However, as indicated by Van Zee et al. [41], the possible clinical utility of the soluble TNF receptors could be severely limited by their short half-life (minutes), and by the fact that the active TNF-α circulates as a trimeric molecule and it is necessary to block at least two of its components to inactivate it. To overcome these shortcomings, recombinant TNF-α receptors have been linked to the FC and hinge regions of a human IgG molecule (TNFR:Fc) [42]. Two clinical trials tested the hypothesis that these fusion molecules could be useful in septic patients. In the first trial, the TNFR II:Fc was administered to patients with septic shock in three different dosages vs. placebo [43]. Even if a dose-response relation between treatment and mortality was observed, no difference of mortality could be demonstrated between the control and the three treatment groups. Moreover, an excess mortality was observed in patients with Gram+ infections receiving the highest dosage. Another clinical trial was then performed, using the fusion molecule TNF I:Fc, again at three different dosages vs. placebo [44]. The study involved 498 patients with severe sepsis and septic shock. The patients treated with the lowest dosage presented an excess mortality as compared with the other groups, and this arm of the study had to be discontinued at an interim analysis. Overall, there was a non-significant trend toward reduced 28-day mortality in all treatment groups. However, a preplanned logistic regression analysis to assess the effects of treatment on 28-day mortality by means of predicted mortality and plasma IL-6 levels, revealed significantly improved survival in patients with severe sepsis who received TNF I:Fc at the highest dosage as compared with the placebo group.

Other investigations involved the antagonism of the PAF, which is a low molecular weight phospholipid produced by macrophages under the influence of endotoxin [45]. Experimentally, the administration of PAF is associated with the hemodynamic and metabolic features of septic shock [46], including hypotension, tachycardia, the increase of microvascular permeability, a negative inotropic effect and the margination and aggregation of leukocytes and platelets. A number of natural as well as synthetic PAF inhibitors have so far been identified. Some of them underwent both experimental and clinical evaluation, shedding some light on the effects of PAF in various target tissues. In rats given endotoxin, the appearance of patchy necrotic bowel lesions is associated with a TNF-induced increase in PAF secretion [47]; these lesions were prevented by pretreatment with a specific PAF antagonist [48]. In healthy volunteers treated with a PAF antagonist 18 hours before the i.v. administration of endotoxin, a reduced cardiovascular, metabolic and hormonal response was observed, in the absence of significant changes of sepsis mediators in the serum [49]. A large randomized, multicenter placebo-controlled, double-blind clinical trial has recently been performed using the PAF receptor antagonist BN 52021, which was

administered at a dosage of 120 mg every 12 hours for 4 days [50]. There was a non-significant improvement in the 28-day survival rate in the treatment group as compared with the placebo group. However, when subgroups of patients were analyzed separately, a significant reduction of mortality was observed in patients with Gram- infections, either shocked or not. Conversely, no difference in the outcome was demonstrated between the placebo and the treatment groups in the absence of a Gram- sepsis.

Lights and shadows of blood purification techniques

A 34-year old man was admitted to the ICU after emergency surgery for recurrent rupture of pulmonary emphysema bullae. An upper right lobectomy was performed, but the patient was not able to resume spontaneous ventilation due to the occurrence of respiratory distress. Blood cultures were positive for Serratia marcescens. Sepsis was further complicated by the occurrence of acute renal failure (creatinine = 8.5 mg/dl). Hemodialysis was then started, which was poorly tolerated and had to be discontinued, and continuous arterio-venous hemofiltration (CAVH) was implemented, allowing the liberal administration of fluids, medication and total parenteral nutrition. Despite maximal support, the patient died from MODS after 93 days in the ICU.

There is experimental and clinical evidence suggesting that septic mediators can to a certain degree be removed by some extracorporeal depuration techniques originally developed for the treatment of acute renal failure – such as continuous arterio-venous and veno-venous hemofiltration (CAVH and CVVH), and continuous arterio-venous and veno-venous hemodiafiltration (CAVHD and CVVHD) – and immunologic and other heterogeneous disorders, such as plasma exchange (PE).

Several experimental studies were devised to evaluate the effects of these techniques on sepsis-induced cardiorespiratory derangements.

On the whole, these studies demonstrated that in septic animals hemofiltration was associated with an improvement of cardiovascular function and a reduction of extravascular lung water, regardless of a change in blood volume [51-53]. Interestingly, the fluid means of hemofiltration removed from the septic animals, but not that drawn from normal controls, was able to reduce myocardial contractility in other healthy animals [54, 55]. In another model of Gram+ sepsis, treated with CAVH at three different levels of plasma filtration (5.5%, 16.6% and 33.4%, respectively), an increased survival time paralleled the increase of depuration efficiency [56].

With the aim of investigating a more effective depuration technique, several studies focussed on PE. Results have again been controversial. Experimentally, Natanson et al. [57] observed a detrimental hemodynamic effect of machine-driven PE as compared with the controls, treated with sham PE. On the contrary, in another animal model of sepsis, Busund et al. [58] reported hemodynamic im-

provement and a higher survival rate in animals treated with PE and fresh frozen plasma transfusions (FFP), as compared with the control group; furthermore, these authors observed a decrease of both TNF and IL-1 in the PE group, whereas in the group treated with FFP only a decrease of the TNF was observed. In another experiment, the same authors attributed the increased mortality rate associated with PE or FFP transfusions to the negative inotropism associated with the depletion of ionized calcium [59]. The clinical application of hemopurification techniques paralleled the experimental investigations, as several authors observed both an improvement of cardiorespiratory function and an increased survival in patients with different cardiovascular disorders treated with these techniques. Gotloib et al. [60] demonstrated an improvement of hemodynamics and gas exchanges in patients with septic ARDS treated with HF, which occurred independently from the removal of fluid. They also demonstrated that some substances involved in the septic process, including endorphines and arachidonic acid derivatives, had a high sieving coefficient through the filter membrane, and related the beneficial cardiorespiratory effects associated with HF to their removal. Better hemodynamic cardiovascular performance was observed by Coraim et al. [61] in patients with low cardiac output after cardiac surgery treated with CAVH, and attributed this effect to the removal of myocardial depressant factors generated during the cardio-pulmonary bypass (CPB). In septic patients, Berlot et al. [62] demonstrated that PE was associated with a significant improvement of the increase of LVSWI, CI, DO_2 and $\dot{V}O_2$ and that these changes were more marked in patients whose cardiac function was more depressed before treatment; however, these changes were not associated with an improvement of mortality. These beneficial effects have been mainly ascribed to the removal of septic mediators. This hypothesis is indirectly also justified by some studies in which the reduction of mortality of septic patients was associated with increased depuration effectiveness. Storck et al. [63] demonstrated a reduced mortality rate in patients with postoperative ARF treated with pump-driven CVVH as compared with the group treated with CAVH, and hypothesized that this result could be ascribed to the removal of larger amounts of mediators obtained with CVVH. Also Barzilay et al. [64] evaluated the effects of depuration techniques in four groups of septic patients treated conservatively (i.e. without any depuration treatment) or with CAVH, CAVHD and CAVHD associated with PE, respectively. In this latter group, the mortality rate of 36% was significantly lower than in patients treated with CAVH, with CAVHD (respectively 71% and 50%) and in patients who were not treated with any blood purification technique (87%).

In recent years it became possible to assess cytokines in biological fluids, and this prompted some authors to measure these substances both in the blood and in the ultrafiltrate. However, the available studies carry conflicting results. In a group of septic patients with ARF treated with CVVH, Bellomo et al. [65] demonstrated that in 12 out of 18 patients (66%) the serum of both TNF and IL-1 decreased not significantly 4 and 24 hours after the treatment had been started,

respectively. Other studies, however, failed to confirm these findings. In septic patients treated with CVVH, Heering et al. [66] did not observe any significant decrease of circulating TNF-α, even if the treated patients presented an improvement of hemodynamics. The same results have been reported in another study, in which hemofiltration performed in patients with early-onset SIRS was associated with an increased clearance of IL-6, even if both blood IL-6 and TNF-α levels remained unchanged [67]. These studies indicate that in septic patients a) blood depuration techniques are usually associated with an improvement of cardiorespiratory performance, which has been largely attributed to the removal of septic mediators, but b) measurement of these substances in patients treated did not provide conclusive evidence, resulting diminished in some investigations and unaltered in others; moreover, c) their real impact on the outcome remains to be established. Although these apparently mutually exclusive findings are difficult to explain, it is nonetheless possible to formulate some hypotheses. Firstly, some mediators could be produced during blood-filter interaction [68]. Actually, Byrick failed to demonstrate a drop in serum TNF levels in patients undergoing CAVHD due to rhabdomyolysis-induced ARF [69]. On the contrary, TNF increased both in the blood leaving the filter and in systemic circulation (from 646 to 765 pg/ml) after 18 hours since the treatment was started, but was undetectable in the ultrafiltrate. Secondly, some mediators circulate bound to other plasma protein; the resulting molecular weight being higher, trans-membrane passage is impaired [70, 71]. Thirdly, the release of septic mediators may not be constant; actually, blood levels of endotoxin TNF fluctuate during the clinical course of septic patients and can be influenced by several factors, including the administration of antibiotics [72, 73] or the occurrence of hypotension [74]; moreover, at least in some studies, it may be that TNF and other cytokines have been measured in different phases, leading to conflicting results. Finally, excessive attention may have been paid to the "wrong" mediators: Hoffmann et al. [75] have recently demonstrated that in septic patients treated with hemofiltration improved cardiovascular function was associated with a reduction of C3a and C5a, in the absence of any significant change of TNF-α, IL-1, IL-6 and IL-8. On the basis of current evidence, it can be concluded that CVVH does not remove a substantial amount of TNF, but can be associated with a substantial decrease of other more distal mediators involved in the pathogenesis of SIRS and MODS [76]. More powerful techniques, such as PE or derived techniques, may effectively remove all mediators, due to the higher cut-off value of the membranes. However, the real effect of these techniques on the prognosis of septic patients without acute renal failure is not yet clear.

Lights and shadows on blood cytokine measurement

A 65-year old woman was admitted to the hospital after 7 days of fever and vomit, with the diagnosis of renal colic. Eight hours after the admission the patient became hypotensive (90/50 mmHg). Coagulative abnormalities were also

present. Abdominal US and CT scans revealed right pyonephrosis. The patient was operated on, and a nephrectomy was performed. In the postoperative period the patient developed severe hypoxemia despite mechanical ventilation at 60% FiO_2 and with a PEEP of 10 cm H_2O for 24 hours. The initial blood lactate level was high (2,5 Mmol/L) and remained elevated for 6 days. Blood TNF and IL-6 values were also elevated, suggesting a poor prognosis. However, after draining an abdominal purulent collection, these values returned to normal and the clinical conditions improved. The patient was then discharged to the surgical ward after 10 days in the ICU.

Many investigations have concentrated on the correlation between the time course of the blood concentrations of sepsis mediators and the outcome. Once again, the results have not been unequivocal. Some authors demonstrated that blood levels of TNF remained elevated in septic patients who ultimately developed MODS and died, as compared with patients whose conditions improved [77, 78]. However, other studies did not confirm these findings [79].

It would therefore seem that the most appropriate method to monitor the evolution of SIRS and sepsis is far from been elucidated, as most of the currently used indicators of the inflammatory response, such as body temperature, white cell count, erythrocyte sedimentation rate or C-protein concentration, are unspecific parameters with changing reliability. Recent studies have shown that IL-6 has a role in the activation of the acute phase response in the liver. IL-6 is produced by various cells, including monocytes, macrophages, and lymphocytes. IL-6 is thought to be the most important mediator of the inflammatory response, and it is also of prognostic value in sepsis and burns [80]. Tissue injury leads to local production of IL-6 and other cytokines that mediate most of the systemic aspects of inflammation [81]. IL-6 is a candidate as a laboratory test that rapidly normalizes after uncomplicated surgery or trauma. In patients undergoing scheduled surgery, the IL-6 serum value rose within 2-4 hours after the intervention, and its peak value varied in the various surgical groups, since the response was related to the duration of surgery and the degree of tissue trauma [82]. Other authors noted a concentration of IL-6 peaks between 4 and 6 hours after surgery and/or trauma, but there is a poor correlation with blood loss, fever, white cell count or duration of surgery [83]. Conversely, its value is well related to the occurrence of infections in the postoperative period [84]. In patients with severe infections, initial high serum levels of IL-6 have been related to the severity of sepsis and the mortality [85].

Procalcitonin (PCT) is an innovative diagnostic variable with features different from other presently available indicators of the inflammatory response. The amino acid sequence (116 aa) of PCT is identical to the prohormone of calcitonin. In the normal and healthy individual, hormonal active calcitonin is produced and secreted by C-cells of the thyroid gland after specific intracellular proteolytic cleavage of the prohormone. PCT is selectively induced during bacterial inflammation, and also in sepsis and MODS. PCT is only induced as a response to systemic infection. Bacterial colonization, capsuled abscesses and

limited local infections in fact do not induce PCT. The amount of PCT induced and the increase of plasma levels are correlated with the extent of the inflammatory reaction. At the end of the acute inflammatory reaction, PCT concentrations immediately decrease according to their plasma half-life times. It has been demonstrated that endotoxin injection into normal subjects results in PCT secretion in the absence of an increase in calcitonin [86]. The PCT produced under an infective stimulation is most likely not produced by C-cells of the thyroid, and neuroendocrine cells of the lung or of the gut are indicated as the possible sources of PCT. In humans PCT is detectable after endotoxin injection at 4h, with peaks at 6h [86]. PCT rises heavily during sepsis in children, and was within or slightly above the normal range in patients with peripheral, local or viral infection [87]. The PCT serum value is clinically related to pulmonary injury [88].

In our study we evaluated eleven patients (7 males, 4 females, age = 68.9 y, 52-82 y) undergoing major surgery, and twelve patients (7 males, 5 females, age = 58.16 y, 16-80 y) with SIRS according to ACCP/SCCM criteria [2]. In the patients undergoing surgery, the blood samples were collected before anesthesia (basal) and after surgery. In the SIRS patients blood samples were collected every 24 h after admission to the Intensive Care Unit.

The data are summarized and expressed as mean and range in Table 1.

Table 1.

	PCT (ng/ml)	IL-6 (pg/ml)
Basal	0.136 (0.025-0.53)	11.84 (0-44.59) a, g
After surgery	0.252 (0.038-0.341) b	252.787 (119.74-1517.766) a
SIRS 24 h	9.58 (0-336) b	293.503 (76.6-15000) g
SIRS 48 h	4.54 (0-420)	215.715 (21.8-11139)
SIRS 72 h	3.755 (0-304)	139.61 (7.45-2168)

a Wilcoxon test: $p = .0033$
b Mann-Whitney U test: $p = .0007$
g Mann-Whitney U test: $p = .0001$

Our data demonstrate that the IL-6 level in postoperative patients with SIRS was significantly higher than the basal value. The patient groups are not similar, but the group undergoing major surgery may be considered a control group: there was no occurrence of fever, white cell increase or other signs of inflammation. The IL-6 value decreased rapidly in this group, as opposed to the trend observed in the SIRS group. PCT increased heavily in SIRS, but not after uncomplicated surgery. Much higher cytokine concentrations were found in the peritoneal fluid than in the plasma, which suggests that the postoperative cy-

tokine response may to a large extent originate from the peritoneal cavity [89]. A local cytokine response may stimulate mesothelial cells and later induce chemotaxis of neutrophils and a further production of cytokines. Peritoneal cytokines may be absorbed into the portal and systemic bloodstream and stimulate the production of acute phase protein by hepatocytes. In SIRS, IL-6 is higher than in the normal control group and may be related to the prognosis [90]. Recently, some authors have demonstrated high serum levels of PCT in severe accidental injury as a sign of a serious inflammatory state [91]. In our SIRS group, the PCT is 90 times higher than normal. The high value of IL-6 in SIRS is similar to that in severe accidental injury. The strongly associated high values of PCT and IL-6 ($r = .844$, $p = .0001$) indicate a heavy reactive inflammatory condition, which may be related to respiratory failure. PCT does not increase postoperatively because of the absence of inflammatory states, while there is a release of cytokines which represents the physiological response to injury [5]. A recent paper indicates PCT in association with the measurement of nitrite/nitrate ratio as the most suitable test for defining patient with septic shock. PCT did not increase in patients with such inflammatory conditions as cardiogenic shock or bacterial pneumonia. Compared with TNF or IL-6, PCT had better sensitivity, specificity and predictive value for positive tests, and predictive value for negative tests [92].

Lights and shadows on the selective decontamination of the digestive tract

What is SDD?

The term systemic digestive decontamination (SDD) has been extended to different protocols aiming at preventing infections due to potentially pathogenic micro-organisms (PPMs) in critically ill patients. Several authors who were disappointed with SDD did not use an appropriate SDD protocol. The full SDD protocol comprises four components: a combination of selected non-absorbable antimicrobials, parenteral antibiotics, a high standard of hygiene, and surveillance cultures [93-95].

Secondary endogenous infections caused by PPMs not carried in the throat and/or gut on ICU admission, but acquired during ICU stay, can be prevented by non-absorbable antimicrobials administered topically in the oropharynx and gut. Polymyxin E, tobramycin and amphotericin B (PTA) is the most frequent association: a 2% paste or gel of PTA is applied to the oropharyngeal mucosa four times a day, and 9 ml of suspension containing 100 mg of polymyxin E, 80 mg of tobramycin and 500 mg of amphotericin B is administered in the digestive tract four times a day. In studies in which lower doses of polymyxin E or other aminoglycosides, quinolones, macrolides, or polyenes were used, or where sucralfate was employed, PPMs were difficult to eradicate [96-98]. This regimen

has been shown to eradicate aerobic Gram-negative bacilli (AGNB) and to reduce fecal endotoxin concentration in healthy human volunteers [99].

Primary endogenous infections, i.e. infections caused by PPMs carried in the throat and/or gut on ICU admission, will be prevented if, for the first four days, such parenteral antimicrobials as cefotaxime or ceftazidime (if patients are suspected of carrying Pseudomonas) are added at a daily dosage of 100 mg/kg.

Both parenteral and topical antimicrobials cannot control exogenous infections, because these infections are caused by micro-organisms introduced directly into the internal organs without previous carriage. High standards of hygiene are necessary to prevent these infections.

Surveillance samples of throat and rectum represent the fourth component of the full SDD protocol. In general, the surveillance set is comprised of throat and rectal swabs taken on admission and afterwards twice weekly. They are processed semiquantitatively to determine the carriage level of PPMs. They monitor the effectiveness of the PTA protocol, assess the level of hygiene of the unit, allow the identification of the type of infection, and determine the intrinsic pathogenicity index for a micro-organism [100].

What SDD cannot do

The aim of the full SDD protocol is to prevent and/or eradicate oropharyngeal and intestinal carriage of both "community" and "hospital" PPMs, leaving the indigenous flora undisturbed. Methicillin-resistant Staphylococcus aureus (MRSA) is intrinsically resistant to the antibiotics commonly used in SDD. Surveillance cultures can detect early MRSA carriage so that topical 2% vancomycin may be used together with skin disinfection with 2% aqueous chlorhexidine.

Moreover, infections due to low pathogens, such as viridans streptococci, coagulase-negative staphylococci (CNS), enterococci and anaerobes, are not prevented by SDD. An increase in CNS and enterococcal carriage may be common is SDD treated patients [101].

Which patients may benefit from SDD?

SDD is one of the few maneuvers in the ICU subjected to scientific and statistical appraisal. It has been evaluated in approximately 50 controlled studies, and its effects have been assessed in several reviews and meta-analyses.

All meta-analyses showed a significant reduction in respiratory tract infections in the SDD group, with a marked effect in patients treated with topical plus systemic antimicrobials (up to 60%) [102-104]. Urinary tract infections, bacteremia and wound infections were also reduced in SDD patients [105, 106]. Full SDD protocol significantly reduced mortality by around 20% [102-104]. No trial included in the most complete meta-analyses showed a significant harmful effect of SDD [102-104].

The full SDD protocol will be useful in critically ill patients admitted to the ICU for (surgical) trauma, burns, acute pancreatitis or liver failure, or acute deterioration of the underlying disease (e.g. chronic obstructive pulmonary disease, cardiac failure requiring more than 3 days of mechanical ventilation) [93-95]. SDD without parenteral antibiotics may be useful in patients submitted to elective major abdominal or thoracic surgery [93-95]. Two days before surgery the patient receives PTA; at the induction of anesthesia, a proper parenteral antibiotic prophylaxis will be administered. This prophylaxis has been shown to reduce morbidity and mortality in esophageal, cardiac, and gastric surgery and liver transplantation [107-109].

Lights and shadows on the surgical approach to the septic patient

A 37 year-old man was admitted to the surgical department for acute pancreatitis. The radiological examination revealed the presence of two cysts in the pancreas. The patient presented a progressive respiratory insufficiency ($PaO_2 < 40$ mmHg) associated with hypotension and leukocytosis (WBC 17,500/ml). An aggressive treatment was instituted, which included mechanical ventilation, the insertion of a Swan-Ganz catheter and percutaneous drainage of the pancreatic collections. Despite this approach, the patient developed ARDS associated with oliguria. Blood cultures were positive for Ps. aeruginosa. Continuous arterio-venous hemofiltration was then implemented, and the clinical conditions improved in two weeks, with the full recovery of the respiratory, renal and pancreatic functions.

The conventional surgical approach to intra-abdominal infections includes laparotomy, drainage of fluid collections, peritoneal lavage, removal of septic foci and closure of the abdominal wall. The source of sepsis must be accurately researched, and involved organs should, if possible, be removed (cholecystectomy, appendectomy, etc.) or sutured. Non-viable tissues should be eliminated, and the hemostasis must be extremely accurate to avoid hematomas which could become foci of secondary infections. Intestinal anastomoses should be avoided due to the high risk of delayed leaking of sutures. Exteriorization of the ansae is highly recommended. The main limitation of conventional treatment is the failure to clear completely all septic foci, which ultimately leads to the occurrence of postoperative intra-abdominal abscesses, possibly causing septic shock and MODS. It is therefore clear that the early diagnosis of postoperative complications is of paramount importance in patients with previously treated intra-abdominal infections to prevent the deleterious effects of poorly drained collections. Re-laparotomy should be considered in three different clinical settings. The first includes peritonitis and firmly documented abdominal abscesses, in which percutaneous drainage is not feasible. Under these circumstances, re-laparotomy is directed toward the definitive eradication of the septic focus. The second indication for re-laparotomy includes postoperative MODS which can-

not be attributed to other causes. In such cases, re-laparotomy has a diagnostic and a therapeutic role. The third indication for re-laparotomy includes the persistence of clinical signs of sepsis despite previous surgical exploration. In these patients, abdominal procedures are scheduled every 24-72 hours, depending on the clinical evolution. Abdominal wall closure can be accomplished in the conventional way or by using loose sutures (bridge) or zippers, which reduce the intra-abdominal pressure and facilitate further interventions. When the abdomen will be free of pus and/or necrotic tissues, the re-laparotomies can be discontinued, even in the presence of small fluid collections.

Another option consists of leaving the abdominal surgical wound open [110]. The main drawback of this technique is the need for prolonged mechanical ventilation [111]. Clinical studies report conflicting results: Mughal et al. [112] demonstrated good survival in patients treated with this technique, whereas Anderson et al. [113] did not observe any major effect on the outcome. According to Wittman et al. [114] the indications for the open approach are:

- diffuse peritonitis associated with conditions which impede the complete eradication of the septic focus or the surgical removal of the involved organ(s);
- diffuse peritonitis lasting > 48 hours;
- diffuse peritonitis of multiple abdominal abscesses in patients with MODS or rapidly worsening clinical conditions.

The open approach has several advantages, including daily surveillance which requires only minimal sedation and prevents increased intra-abdominal pressure, which can have deleterious effects on the renal function. Some limitations do however exist, including the need for a prolonged stay in the Intensive Care Unit, the fluid loss, the ileus pain, and the risk of such post-procedural complications as fistulas, laparocele, bleeding and the perforation of abdominal viscera.

The open approach can be performed with different techniques. The simplest consists in leaving the wound open, which is covered with a sterile dress. The more widely used technique utilizes a non-absorbable biocompatible net, which is sewed to the edges of the surgical wound. The open approach may be limited to some intra-abdominal compartment, such as the lesser sac, during severe acute infected pancreatitis.

Conclusions

Despite major progress in the understanding of the pathophysiologic mechanisms linking an initially circumscribed infection (i.e. pneumonia) to the development of sepsis and MODS, the survival of patients with these systemic disturbances is still poor. This could be ascribed to several factors, including a) a relatively late diagnosis, caused by the time gap existing between the triggering of

the mediator network and the occurrence of tissue damage and the onset of symptoms; b) the side effects of commonly adopted therapeutic measures (i.e. certain antibiotics), which may in many cases be considered a double-edged sword, and c) still insufficient recognition of individual functional reserves, which even the most advanced treatments tend to leave untouched. In our opinion, the results of the large clinical trials with anti-mediator agents only added further to the confusion, as mortality rate in highly complicated patients, such as those with sepsis and MODS, is a rather rough endpoint to verify the effectiveness of a treatment, and clinical and underlying conditions of the patients enrolled in these trials were too different.

In the treatment of septic patients, the shadows stretching out between the areas of light are still far from being illuminated – unless more appropriate endpoints are chosen, and really comparable patients are enrolled in clinical trials.

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