SEPTIC SHOCK

Edited by

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Preface

Shock complicating bacteremia presents one of the most dramatic constellations of clinical problems that a clinician must recognize, diagnose, and treat. While bacteremic shock has been known and feared by clinicians for at least a century, its incidence has risen sharply since the classical descriptions of gram-negative sepsis by Max Weill and his coworkers in the late 1950s. Today it is recognized as a particularly unfortunate complication of modern medical technology and hospitalization for other, unrelated problems.

This volume takes a fresh look at a number of features of the septic shock syndrome, ranging from pathogenetic mechanisms and newer diagnostic modalities to rational treatment with both antimicrobial agents and supportive care. It concludes with a summary of the role of immunotherapy and immunoprophylaxis. To the knowledge of the editors, no well-referenced compilation of this type of information written for both investigators in the field and practicing clinicians is currently available.

In the discussion of pathogenetic mechanisms, it is emphasized that factors from both microbes and the host must be taken into consideration. Gram-negative endotoxins, cell wall components of gram-positive bacteria, and fungi can have direct effects or, more importantly, can trigger host–mediator systems responsible for the consequences of septicemia and septic shock. The potential role in pathogenesis of the complement system, polymorphonuclear leukocytes, and humoral mediators emphasizing, in particular, newly recognized metabolites of arachidonic acid and opiate peptides is discussed in detail. The apparent paradoxical role that mucosal IgA antibody plays in both protecting against as well as promoting susceptibility to bacteremia is presented. Pulmonary injury culminating in the adult respiratory distress syndrome is a common complication of septic shock, and current understanding of the pathogenesis of this complication is highlighted.

With a clear understanding of pathogenetic mechanisms the clinician can develop rational approaches to the diagnosis and therapy of sepsis and septic shock. Newer microbiologic methods for diagnosis are compared to time-honored blood culturing techniques. A rationale for the utilization of broad-spectrum or synergistic combinations of antimicrobials is developed, and newer antimicrobial agents are placed in context with older compounds. A major area of controversy that relates to the efficacy and role of glucocorticoids in the treatment of septic

Contents

1 Epidemiology and Overview of the Problem

Jay P. Sanford

"In acute diseases, coldness of the extremities is a very bad sign."[1] While these clinical features, which might well have been septic shock, were recognized as early as 400 BC by Hippocrates, in this discussion of newer concepts in pathophysiology and treatment more precise definitions must be used. The term "septicemia" or "sepsis" is rather imprecise, but it implies bloodstream invasion either by bacteria or absorption of toxic materials produced by bacteria with overt, usually severe, clinical symptoms or signs, including those of systemic toxicity. When associated with signs of poor tissue perfusion, the term "septic shock" is used. By this definition, septic shock may be the consequence of a number of pathogenic mechanisms (Table 1-1). Recognizing these diverse mechanisms, it may be more useful clinically to consider specific organisms or disease syndromes that can be associated with septic shock; these etiologic agents and pathogenic mechanisms are listed in Table 1-2.

Osler noted, "The organisms producing septicemia are, as a rule, those of suppuration—namely, the forms of streptococci and staphylococci."[2] However, it has become common to apply the term "septic shock" to the shock state associated with infection due to gram-negative bacteria. Further, within this definition, except in neonatal sepsis, a number of gram-negative organisms that may cause shock are excluded. Diseases usually excluded are meningococcemia, typhoid, cholera, and other enterotoxin-mediated diarrheal diseases, plague, and infections caused by *Haemophilus influenzae*. Some of these exclusions, such as plague, appear to be caused by the same pathogenic mechanisms as are the Enterobacteriaceae and Pseudomonadaceae.[2,3] As pathophysiology and treat-

Table 1-1. Shock Associated with Infection. Pathogenic Mechanisms

Primary pump failure (cardiogenic)
  Viral: coxsackievirus
  Bacterial: diphtheritic myocarditis, leptospirosis
  Parasitic: *Toxoplasma gondii*
Failure of myocardial filling (pericardial effusion)
Inadequate intravascular volume
  Extracellular fluid loss secondary to diarrhea or sequestration
    Cholera, enterotoxic *Escherichia coli*, *Vibrio parahemolyticus*
    Pancreatitis
  Increased vascular permeability
    Rickettsial diseases: Rocky Mountain spotted fever
    Viral hemorrhagic fevers: arenavirus, dengue, hemorrhagic shock syndrome
Failure of venous return (intravascular pooling)
  Gram-negative bacillary bacteremia
  Candidemia
Hypoxemia
  Pneumonia: viral, bacterial
  Adult respiratory distress syndrome: gram-negative bacillary bacteremia
  Profound intravascular hemolysis: clostridial

Table 1-2. Etiologic Agents and Pathogenic Mechanisms That Can Cause Septic Shock

Classification of Etiologic Agents	Specific Microorganisms/ Diseases	Pathogenic Mechanism[a]
Gram-positive cocci	Staphylococcal "food poisoning"	Enterotoxin Hypovolemia
	Toxic shock syndrome	(?) Exotoxin C and or/ enterotoxin F
	Pneumococcal pneumonia	No toxin known Hypoxemia Pericardial tamponade
	Post-group A streptococcal carditis (acute rheumatic fever)	Toxin not proven Myocarditis
Gram-positive bacilli	Diphtheria	Exotoxin (inactivates transferase II) Myocarditis
	Anthrax	Exotoxin Hypovolemia 2nd to fluid translocation
	Clostridial myonecrosis	Multiple exotoxins Hypovolemia 2nd to fluid translocation Hypoxemia 2nd to intravascular hemolysis
Gram-negative cocci	*Neisseria* spp., meningococcemia, gonococcemia	Endotoxin
Gram-negative bacilli	"Coliforms"	Endotoxin
	Pseudomonas aeruginosa	Exotoxin (inactivates transferase II) Endotoxin
	Brucellosis, typhoid fever	Endotoxin
	Plague	Endotoxin
	Cholera, enterotoxigenic *Escherichia coli*, non-cholera vibros	Enterotoxins Stimulates adenylate or guanylate cyclase with electrolyte secretion

(continued)

Table 1-2. Etiologic Agents and Pathogenic Mechanisms That Can Cause Septic Shock (continued)

Classification of Etiologic Agents	Specific Microorganisms/ Diseases	Pathogenic Mechanism[a]
	Bacteroides fragilis	Unknown Septic pulmonary emboli Hypoxemia
	Fusobacterium sp.	Endotoxin
	Legionnaires' disease	(?) Exotoxin (?) Endotoxin Hypoxemia
Spirochetes	Syphilis, Jarisch-Herxheimer reaction	(?) Endotoxin
	Relapsing fever (*Borrelia* sp.)	Endotoxin
	Leptospirosis	Endotoxin Myocarditis Hypoxemia 2nd to intravascular hemolysis
Rickettsia	Rocky Mountain spotted fever, typhus (louse-borne)	Exotoxin Increased capillary permeability with fluid translocation (?) Antigen–antibody reaction Increased capillary permeability
Viral	Hemorrhagic fevers	Toxin not proven Hypovolemia 2nd to increased capillary permeability
	Coxsackievirus B	Toxin not proven Myocarditis
	Viral pneumonia, influenza, varicella, respiratory syncytial virus	Toxin not proven Hypoxemia
Fungal	Candidemia	Endotoxin
Parasitic	*Toxoplasma gondii*	Toxin not proven Myocarditis
	Pneumocystis carinii	Toxin not proven Hypoxemia
	Trypanosoma cruzi	Toxin not proven Myocardiopathy

2nd = secondary.

[a] In many instances the pathogenic mechanism(s) underlying the shock state is unknown and a probable mechanism is suggested.

ment are reviewed, it is important to reconsider the appropriateness of such exclusions. "Endotoxic shock" has been used as an alternative term; however, controversy exists as to its correctness.[4]

HISTORICAL BACKGROUND

The association of severe infections with circulatory failure, hypotension, and poor tissue perfusion has been known for many years. Osler[5] wrote of a "typhoid state" occurring in patients with pyelitis in which death occurs, and

Boise[6] wrote on the differential diagnosis of shock, hemorrhage, and infection. Jacob[7] reviewed 39 cases of *Escherichia coli* sepsis, of which 13 were his own; 16 of these patients died (41 percent). The portals of entry in order of decreasing frequency were the biliary tract, the urinary tract, the gastrointestinal tract, and the female genital tract. In 1924, prior to the introduction of sulfonamides or antibiotics, Felty and Keefer[8] reported a 32 percent mortality for patients with bacteremia due to *E. coli*.

Concurrently, it was recognized that dead bacilli and their products could produce hypotension when given intravenously. Intravenous typhoid vaccine produced a fall in blood pressure lasting several hours.[9,10] A serious form of hypotension, persisting for several days, was observed after intravenous administration of a tumor-necrotizing polysaccharide derived from *Serratia marcescens* to patients with advanced neoplasms.[11] A pyrogen derived from *Pseudomonas aeruginosa* was used in the treatment of malignant hypertension.[12]

In the early 1950s it became widely appreciated that gram-negative bacilli could produce fatal hypotension when bacteremia occurred as a complication of infection elsewhere in the body.[13,14] Of 1396 blood cultures obtained from 980 patients over an interval of nine months in 1950–1951 at the Minneapolis General Hospital, 44 (3.4 percent) were positive.[13] Aerobic gram-negative bacilli were isolated from 25 (57 percent) of the positive cultures. Observing 29 patients, Waisbren[13] described three clinical presentations: asymptomatic (5), toxic (13), or a shocklike state (15), in which the patients were apprehensive, hypotensive, and lethargic, and their skin was cold and clammy. Five of the patients with shock died (33 percent).

INCIDENCE

The incidence of gram-negative bacillary bacteremia has increased strikingly over the past three decades. The best data are those of McGowan and associates,[15] who reported on the occurrence of bacteremia at the Boston City Hospital during selected years between 1935 and 1972. Bacteremia due to gram-negative bacilli was infrequent in 1935, 0.9 cases per 1000 admissions. In 1941 it remained at 1.3 cases per 1000 admissions, but by 1947 had increased to 4.3 cases per 1000 admissions, and reached 11.5 cases per 1000 admissions in 1972.

In 1974, as a result of concern over the suggested magnitude of the problem (300,000 cases in the United States with 100,000 deaths) and a suggested causal relationship with the inappropriate overuse of antibiotics, the Subcommittee on Health of the United States Senate requested that a study group be convened to answer four specific questions[16–18]:

1. What is the incidence of gram-negative bacteremia?
2. What are the factors responsible for the increase?
3. What is the number of deaths attributable to gram-negative bacillary bacteremia?
4. What is the current status of medical treatment?

A Special Study Group on Gram-Negative Rod Bacteremia was appointed. A summary of their findings was reported, but unfortunately the full report was never published.[18] Almost ten years later these same questions provided the format of this treatise.

Similar data have been reported from other university hospitals. McCabe and Jackson[19] observed an increase in incidence from 0.75 per 1000 admissions in 1951 to 3.9 per 1000 admissions in 1958 at the University of Illinois. Subsequently, Kreger and colleagues[20] reported an increase from 7.1 per 1000 in 1965 to 12.6 per 1000 in 1974 at Boston University Hospital. While recent data have not been reported from university hospitals, an incidence of 10 cases per 1000 admissions (1 percent) represents a conservative estimate. The incidence in university-type tertiary care centers exceeds by two- to fivefold that observed in community hospitals. For the years 1970–1978, Scheckler[21] reported an incidence of 1.8 per 1000 admissions to a community hospital in Madison, Wisconsin. The National Nosocomial Infections Study,[22] which involves 82 hospitals, 77 percent of which are nonuniversity, in 31 states, recorded an incidence of 1.5 cases per 1000 discharges among 1,339,415 patients in 1978. More recently, Bryan and colleagues[23] reported an incidence of 3.9 per 1000 discharges in four nonuniversity hospitals. Extrapolation of these data to the entire United States has obvious pitfalls, but on the basis of 35 million admissions yearly to acute care hospitals, between 52,000 to 136,000 cases of gram-negative bacillary bacteremia occur nationally each year. These estimates are virtually the same as those of the Special Study Group, who considered the best estimate of incidence to be 71,000 cases annually in the United States.[18]

MORTALITY

On review of 15 studies that reported overall mortality without stipulating the role of the gram-negative bacteremia in death, there was an average mortality of about 40 percent. However, when the direct causal role of the bacteremia was considered, fatality ratios of 25 and 32 percent were reported.[18] The more recent studies from nonuniversity medical centers have reported mortality specifically attributable to gram-negative bacteremia to be 20 and 19 percent.[21,23]

These figures are striking when one recalls that in the report by Jacob[7] in 1909 the mortality was 41 percent, and Felty and Keefer[8] reported 32 percent in 1924. The advances in antimicrobial therapy and supportive care, including sophisticated cardiovascular support, over the past three decades do not appear to have had a significant impact on mortality due to gram-negative bacillary bacteremia. While it is difficult for most of us today to accept such a conclusion, it is not unique in infectious diseases. Despite the high degree of efficacy of penicillin G in pneumococcal pneumonia, it is known that penicillin therapy does not decrease mortality in the first 24 hours below that observed in the prepenicillin era. As pointed out clearly by Maunder and Carrico in Chapter 16, in most forms of circulatory shock the primary problem is an abnormality of the circulation, which produces cell injury. The situation in septic shock is the opposite; it is

reasonable to propose that the cell injury is the primary problem and that the classic circulatory derangements associated with septic shock are very late findings.

EPIDEMIOLOGY

A review of the epidemiology of gram-negative bacillary bacteremia is appropriate to provide background as to the host and bacterial factors that appear to be of importance not only in occurrence but in outcome. Further, an understanding of the epidemiology provides approaches to prevention of colonization with gram-negative bacteria.

Members of the family Enterobacteriaceae are normal endogenous microorganisms within the lower gastrointestinal tract. Coliforms are isolated from less than 5 percent of cultures of the oropharynx or skin of normal individuals.[24] Enterobacteriaceae, members of the family Pseudomonadaceae, and multiple other species of gram-negative bacilli are present in the environment, in water, in soil, and on plants (Figure 1-1).

Escherichia coli is the most common aerobic gram-negative bacillus within the colon of normal persons. Such *E. coli* tend not to contain plasmids that produce β-lactamases, hence are usually susceptible to most penicillins and cephalosporin antibiotics.

In discussions of epidemiology and treatment, a distinction is made between community-acquired and hospital-acquired infections. The former are usually caused by *E. coli*, and even if caused by other coliforms these infections are susceptible to most antimicrobial agents. Community-acquired gram-negative bacteremia usually arises from an individual endogenous flora found in the

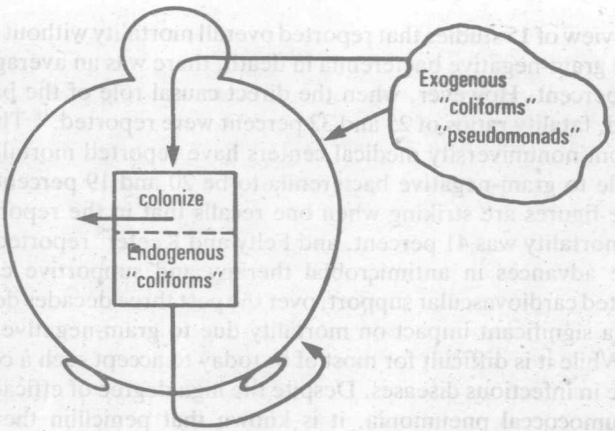

Fig. 1-1 Epidemiology of aerobic gram-negative bacilli. Endogenous organisms may invade or colonize exterior surfaces. Exogenous organisms may colonize exterior or interior surfaces and invade.

urinary, biliary, or genital tract. A urinary tract infection with obstructive uropathy bloodstream invasion is common, and septic shock may ensue. Since such infections arise from the host's endogenous flora, prevention must focus on detection and relief of the obstructive uropathy, or active immunization should be provided where vaccines are available. The proportion of patients in the reported series of gram-negative bacteremia varies greatly. In the study of McCabe and Jackson,[19] one fourth were community-acquired, while in that of Scheckler,[21] two thirds were community-acquired.

A number of factors may result in the ability of coliforms to colonize sites beyond the colon, for example, the oropharynx or skin. Such a phenomenon has been designated loss of colonization immunity. It was recognized the "critically ill" patients often lost their colonization immunity (Table 1-3).[24] The administration of antibiotics to these patients was considered the major cause; we showed that antibiotic administration was not the sole determinant, although it was a significant risk factor (Tables 1-4, 1-5).[24,25] Such critically ill patients are at much greater risk for septic shock because their endogenous load of gram-negative bacteria is increased, and ruptures in defense barriers such as the skin and the cough reflex or neutropenia are more likely to enable ingress of gram-negative bacilli.

In considering the epidemiology, the exogenous "cloud" of aerobic gram-negative bacilli has even greater significance (Fig. 1-1). This cloud may be in the form of another person who has become colonized with resistant or invasive gram-negative bacilli; for example, an individual with an indwelling urethral catheter and collection bag may serve as a source from which multiple other

Table 1-3. Prevalence of Aerobic Gram-Negative Bacilli Isolated on Oropharyngeal Culture

Population	Isolation (%) of Aerobic Gram-Negative Bacilli on Multiple Cultures
Normal (nonhospital associated)	6
Psychiatry inpatients	6
Orthopedic inpatients	35
"Moribund" patients	73

Adapted, by permission of the New England Journal of Medicine, from Johanson WG, Pierce AK, Sanford JP: Changing pharyngeal bacterial flora of hospitalized patients: Emergency of gram-negative bacilli. N Engl J Med 281:1137, 1969.

Table 1-4. Prevalence of Aerobic Gram-Negative Bacilli (GNB) Isolated on Oropharyngeal Culture Related to Antibiotic Administration

Population	No. Patients Receiving Antibiotics	% with GNB	No. Patients Not Receiving Antibiotics	% with GNB
Orthopedic inpatients	14	36	67	31
"Moribund" patients	10	80	13	62

Adapted, by permission of the New England Journal of Medicine, from Johanson WG, Pierce AK, Sanford JP: Changing pharyngeal bacterial flora of hospitalized patients: Emergency of gram-negative bacilli. N Engl J Med 281:1138, 1969, with permission.

Table 1-5. Variables Associated with Colonization of the Respiratory Tract with Gram-Negative Bacilli (GNB) in 213 Patients[a]

Variable	GNB Colonization		
	Yes	No	*p*
Sex			
Men	57	66	
Women	38	52	NS
Smoker			
Yes	56	67	
No	39	51	NS
Coma[b]			
Yes	35	26	
No	60	92	$p < 0.05$
Hypotension[c]			
Yes	19	6	
No	76	112	$p < 0.01$
Sputum present			
Yes	71	46	
No	24	72	$p < 0.001$
Tracheal intubation			
Yes	36	20	
No	59	98	$p < 0.001$
Inhalation therapy			
Yes	88	98	
No	7	20	NS
Antimicrobial drugs			
Yes	38	12	
No	57	106	$p < 0.001$
Arterial pH $\leq$ 7.31			
Yes	33	16	
No	62	102	$p < 0.001$
BUN $\geq$ 50 mg/100 ml			
Yes	10	2	
No	85	116	$p < 0.05$
WBC > 15,000 or < 4,000			
Yes	37	18	
No	58	100	$p < 0.001$
Hb $\leq$ 8 g/100 ml			
Yes	2	1	
No	93	117	NS

From Johanson WG, Pierce AK, Sanford JP: Nosocomial respiratory infections with gram-negative bacilli. Ann Intern Med 77:701, 1972, with permission.

NS, not significant; BUN, blood urea nitrogen; WBC, white blood cells; Hb, hemoglobin.

[a] Patients admitted to a medical intensive care unit.

[b] Defined as loss of consciousness with no response to commands; may respond to painful stimuli.

[c] Systolic blood pressure < 80 mmHg or requiring vasopressors for more than 4 hours.

patients with catheters and collection bags may be cross-contaminated and colonized if careful attention is not paid to hand washing between patients by all personnel. The exogenous organisms may include pseudomonads, which can invade directly from external sources, such as contaminated inhalation therapy equipment, or can colonize patients who have lost their colonization immunity, and then follow the same potential sequences as the endogenous organisms.