Bacteremia Caused by Gram-Negative Bacilli

*Martin C. McHenry, M.D., M.S. (Med.), F.A.C.P.,**
*and William A. Hawk, M.D.***

In the past four decades, bacteremia caused by opportunistic gram-negative bacilli has evolved from a relatively uncommon disorder to a major health problem throughout the world. The incidence continues to rise at an alarming rate, despite the availability of potent antimicrobial drugs. It is estimated that there now may be as many as 100,000 deaths caused by gram-negative bacillemia in the United States each year.[59] Recent evidence suggests that the clinical setting and relative frequency of organisms causing the condition may be changing.[77] Organisms that rarely caused infection in the past have emerged as significant pathogens. Intrahospital and nationwide epidemics of gram-negative bacillemia have occurred. New clinical syndromes, unusual portals of entry, and different mechanisms for development of bloodstream infections caused by those organisms have been documented. New information is available concerning immunologic protective mechanisms against gram-negative infections. The purpose of this report is to review briefly, in view of current developments, selected aspects of the problem of bacteremia caused by opportunistic gram-negative bacilli.

CAUSATIVE ORGANISMS

Although *Escherichia coli* has generally been the most common pathogen responsible for gram-negative bacteremia, members of the Klebsiella-Enterobacter-Serratia group have become the most frequent causes of the condition at some large medical centers.[77] Dupont and Spink[25] noted that the incidence of bacteremia caused by members of that group increased steadily in recent years, whereas the incidence of bacteremia caused by *E. coli* remained relatively constant. Several inves-

*Head, Department of Infectious Disease, Cleveland Clinic Foundation; Assistant Clinical Professor of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio.
**Head, Department of Pathology, Cleveland Clinic Foundation; Assistant Clinical Professor of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio.

tigators have documented the rising incidence of septicemia caused by *Serratia marcescens*,[2, 9] an organism not generally regarded as a pathogen until recently.[21, 23, 100] Data now available from some large hospitals indicate that the incidence of bacteremia caused by *Pseudomonas aeruginosa*[30, 99] and by Proteus[1] is also increasing. Recent reports attest to the frequency and high mortality from polymicrobic bacteremia;[8, 39, 40] gram-negative bacilli are the organisms most frequently involved in such infections. Before 1960, bacteremia caused by members of the Bacteroidaceae was diagnosed infrequently,[66] but in the past decade, the Bacteroidaceae have been shown to be a common cause of bacteremia.[17, 68] This may be due in large part to improved techniques for isolation of anaerobes.[17] Currently, Bacteroidaceae account for 9 to 10 per cent of all positive blood cultures at some medical centers.[17, 101]

Among the less common opportunistic gram-negative bacilli recently identified in septicemias are species of Pseudomonas other than aeruginosa,[33, 35, 82] *Aeromonas hydrophilia*,[22, 43] members of the genus Erwinia,[27, 73] Providence bacilli,[42, 93] *Edwardsiella tardia*,[94] *Hafnia alvei*,[26] *Bordatella bronchiseptica*,[33] and Herellea species.[72]

Those properties of opportunistic gram-negative bacilli which determine their ability to produce serious disease are not well defined. Some of the literature on this subject was reviewed in 1969[60] and will not be repeated here. Recently, Young and associates[43, 103, 104] showed that strains of *P. aeruginosa* and *A. hydrophilia* obtained from bacteremic patients were resistant to the bactericidal action of normal serum. Other workers demonstrated that strains of *E. coli* containing K antigen (envelope antigen) are more invasive than strains lacking this antigen.[36] This may be due to the inhibitory action of K antigens on phagocytosis and on killing of organisms by complement. Some strains of *S. marcescens* produce a proteinase capable of cleaving the third component of complement; it was postulated that this might contribute to the initiation or maintenance of an inflammatory response.[14] Other investigators[74] showed that strains of *S. marcescens* can survive and reproduce within leukocytes. Isolates of Erwinia and *Enterobacter cloacae* are able to persist and multiply in acidic solutions containing high concentrations of glucose, whereas most other organisms do not;[27] this appeared to be an important factor in the development of a nationwide epidemic of septicemias from contaminated intravenous solutions.

Several of the factors of *P. aeruginosa* responsible for pathogenicity have been described by Liu and associates.[5, 51-53] Young[103] demonstrated that heat-stable somatic antigens of *P. aeruginosa* have properties enabling the organism to resist phagocytosis. The exotoxin of *P. aeruginosa* is capable of causing uncoupling of oxidative phosphorylation of susceptible cells.[81] Bacteroides organisms have several factors which may be related to pathogenicity.[17] These include endotoxin, heparinase, collagenase, fibrinolysin, and other proteolytic enzymes, as well as deoxyribonuclease and ribonuclease.

Endotoxins are lipopolysaccharides that form a portion of the cell wall of gram-negative bacteria. The endotoxins of gram-negative bacilli appear to be both antigenic and toxic, and produce a wide variety of biologic effects when injected into experimental animals. Some of the ab-

normalities produced by bacterial endotoxins in animals have been observed in patients with gram-negative bacillemia. These include fever, hypotension, shock, consumption of complement,[55] activation of the kallikrein system and decreases in Hageman factor,[70] hyperlipidemia,[32, 49] elevation of degradation products of fibrinogen and fibrin,[88] and lesions resembling the generalized Schwartzman reaction.[84] Bacterial endotoxin may produce disseminated intravascular coagulation in animals, and disseminated intravascular coagulation has also been documented in some cases of gram-negative bacillemia in humans.[83] A section of the kidney from a patient with fatal gram-negative bacillemia and disseminated intravascular coagulation is shown in Figure 1. Braude and associates[10] recently made the interesting observation that antiserum to bacterial endotoxin prevents the development of disseminated intravascular coagulation in experimental animals.

Although bacterial endotoxin has long been suspected of being a major factor in the pathogenesis and manifestations of gram-negative bacillemia, proof of this hypothesis is lacking. One of the major problems has been the lack of a specific, sensitive assay for bacterial endotoxin in body fluids.

Levin and associates[50] recently reported that endotoxin in low concentrations caused gelation of a lysate of the blood cells (amebocytes) of the horseshoe crab, Limulus. This led to the development of an assay capable of detecting minute amounts of endotoxin in human blood. Levin and associates[49, 50] found a good correlation between positive Limulus tests and infections due to gram-negative organisms. Patients with infec-

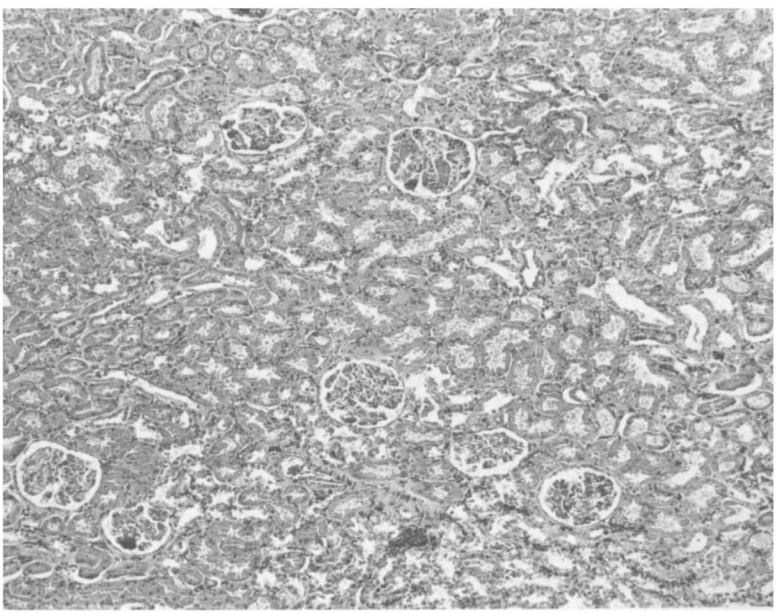

Figure 1. Photomicrograph of glomerular capillary thrombi in kidney of patient who had fatal disseminated intravascular coagulation associated with gram-negative bacillemia. Hematoxylin and eosin stain, ×64.

tions caused by gram-positive cocci had negative results. Hypotension and death occurred twice as frequently in patients with positive Limulus tests compared with patients with gram-negative bacteremia and negative Limulus tests. They suggested that the Limulus test could be used prognostically to define a population with high mortality, and possibly to assist the physician in distinguishing between gram-negative and gram-positive sepsis.

Unfortunately, Stumacher and associates[95] could not confirm these findings. Their Limulus assay system was hampered by both false-positive and false-negative results. The occurrence of shock or fatal outcome in gram-negative bacteremia failed to correlate with this assay for endotoxin. Further studies are urgently needed to resolve these discrepancies.

Lüderitz and associates[54] have reported that the cell walls of most gram-negative bacteria have almost identical lipopolysaccharide core structures, consisting of lipid A and ketodeoxycytonate to which differing O-specific oligosaccharides are attached. Active and passive immunization of animals with this core lipopolysaccharide from a gram-negative bacillus protects them from death after challenge with heterologous strains of gram-negative bacilli.[15, 56] Furthermore, McCabe and associates[59] showed that both shock and death in patients with gram-negative bacillemia were significantly less among patients with high titers of antibody to the core lipopolysaccharide (cross-reactive antibody) than in the group of gram-negative bacteremic patients with low titers of cross-reactive antibody. These studies may provide a basis for an immunologic approach to the prevention of gram-negative bacillemia.[87]

PORTAL OF ENTRY AND PATHOGENESIS: SELECTED ASPECTS

In the preantimicrobial era, the usual sources of bacteremia due to gram-negative bacilli were the genitourinary tract, gastrointestinal tract, and biliary passages.[28] In recent years, other portals of entry have become relatively common including the skin (third degree burns), subcutaneous tissues (postoperative wounds), and lungs (Fig. 2).

According to Finland and Barnes,[29] the incidence of fatal endocarditis caused by gram-negative bacilli appears to be increasing; reviews of this condition have recently been reported.[71, 78, 85] Even more striking has been the high incidence of bacillemia associated with intravenous cannulas.[64, 77] Bacteremia caused by gram-negative bacilli has also been reported as a complication of infected arterial grafts[20] and arteriovenous fistulas.[48] Contaminated intravenous solutions recently have provided mechanisms for intrahospital and nationwide epidemics of septicemia caused by gram-negative bacilli.[13, 24, 27, 86, 98] The clinical course of a patient who had Enterobacter bacteremia secondary to a contaminated intravenous solution is shown in Figure 3. Gram-negative bacillemia has also been one of the expressions of intrahospital outbreaks of infections associated with contaminated respiratory therapy equipment.[61]

Data now available indicate that gram-negative bacillemia occurs frequently after surgical or instrumental procedures on the biliary, gas-

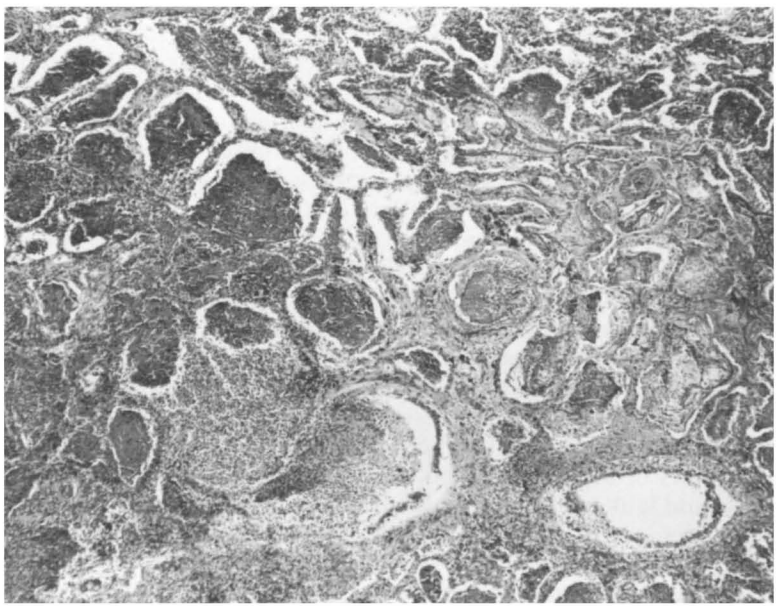

Figure 2. Necrotizing gram-negative bacillary pneumonia which was the apparent source of Klebsiella bacteremia. Hematoxylin and eosin stain, ×40.

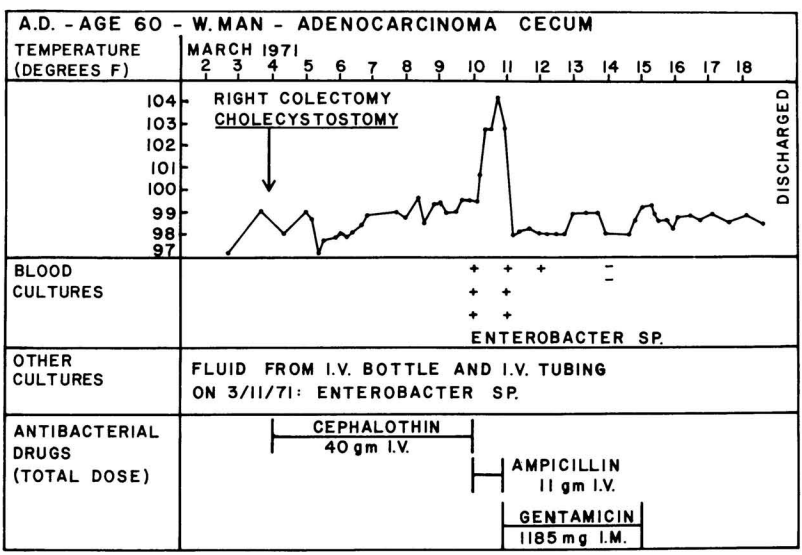

Figure 3. Graphic representation of clinical course of patient who recovered from gram-negative bacillemia secondary to a contaminated intravenous infusion.

trointestinal, or genitourinary tracts.[12, 65, 96] It even may develop after routine sigmoidoscopy[46] or proctoscopic biopsy.[45] Gram-negative bacillemia is also common after septic abortion.[92] Usually these bacteremias are transient and clinically insignificant, but they may have lethal complications. Patients with pre-existing urinary tract infections[96] or positive cultures of bile at surgery[16] appear to be at high risk for development of bacteremia after surgery or instrumentation of the region in question. Data have also been presented suggesting that, in the presence of severe granulocytopenia in patients with leukemia, lymphoma, or carcinomas, the recovery of *P. aeruginosa* in routine surveillance cultures (especially of the rectum) identifies patients who will probably contract bacteremia from those organisms.[90]

The pathogenesis of gram-negative bacillemia in patients with underlying hematologic diseases differs considerably from the pathogenesis of the condition in patients with underlying nonhematologic diseases.[62] In patients with hematologic diseases (e.g., leukemia, malignant lymphoma, aplastic anemia), bacillemia frequently develops without previous surgery or instrumentation. Among the major predisposing factors are profound leukopenia, mucosal ulcerations, administration of adrenal glucocorticoids, and cytotoxic chemotherapeutic agents.

The most frequent portals of entry for bacillemia are the lungs or mucous membranes of the respiratory and gastrointestinal tracts. The lung of a patient with chronic lymphatic leukemia and aplastic anemia who died of fulminating bacteremic pneumonia caused by *P. aeruginosa* and *Diplococcus pneumoniae* is shown in Figure 4. Several bacillary vascular lesions of *P. aeruginosa* are evident in the section. Lesions giving rise to bacteremia in patients with hematologic disease often show evidence of necrosis and inflammation with a paucity of polymorphonuclear leukocytes.

In patients with underlying nonhematologic diseases, leukopenia is not common and lesions usually are suppurative. A section of the kidney of a patient with underlying nonhematologic disease who died of fulminating *E. coli* bacteremia secondary to acute suppurative pyelonephritis is shown in Figure 5. In patients with underlying nonhematologic diseases, the sources of gram-negative bacteremia are more frequently located in the genitourinary tract, peritoneal cavity, or biliary passages than in the lungs or mucosal surfaces. The location of the distributing foci of infection is often related to underlying local anatomic abnormalities (for example, obstruction of the urinary or biliary passages) and antecedent surgical or instrumental trauma.

Bacteremia caused by gram-negative bacilli appears to be a relatively frequent complication in patients with hepatic cirrhosis; it may develop as the result of spontaneous peritonitis[19] or may be secondary to infections of the urinary tract or biliary passages.[69] Gram-negative bacillemia also appears to be a relatively common complication in recipients of renal transplants, and most commonly arises from foci of infection in and about the revised urinary tract.[4, 47, 76] Among the major predisposing factors are heavy immunosuppressive therapy, leukopenia, hypogammaglobulinemia, hyperglycemia, failure of the graft, and complications such as ureteral leakage or postoperative hematomas.

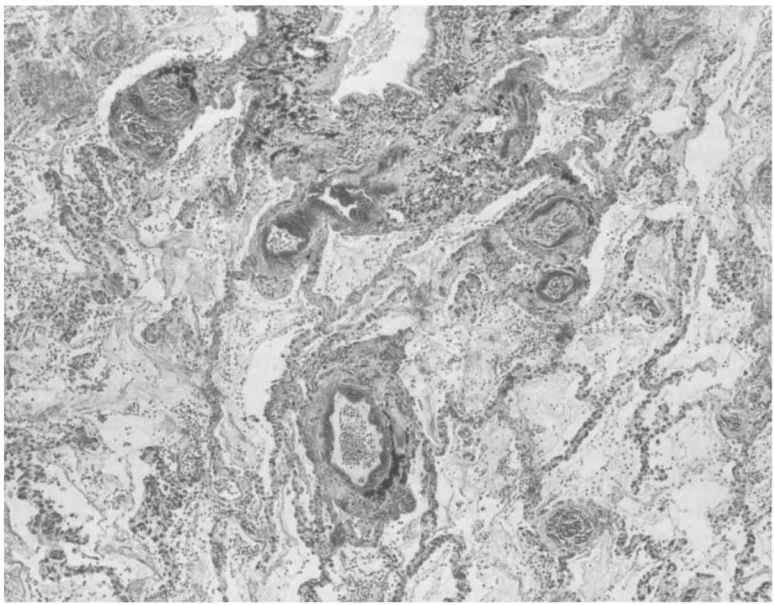

Figure 4. Photomicrograph of pseudomonas bacillary vasculitis in the lung. Hematoxylin and eosin stain, ×64.

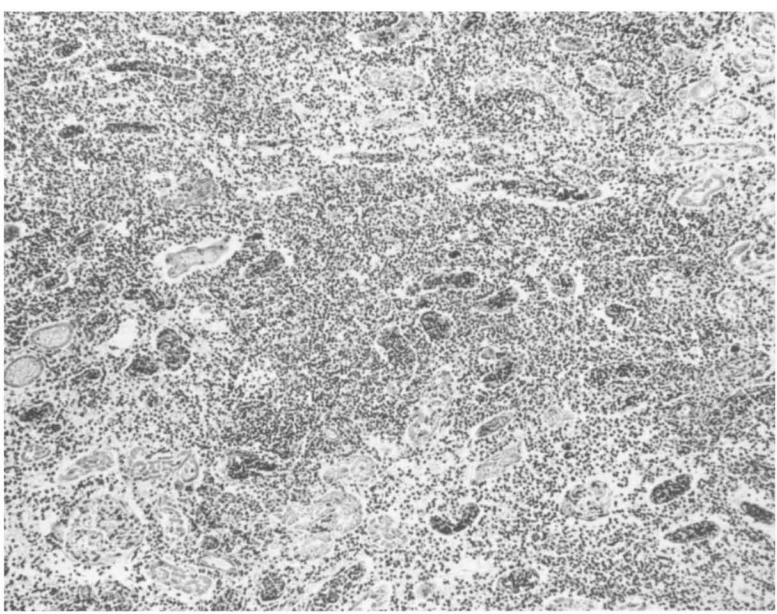

Figure 5. Acute suppurative pyelonephritis. Hematoxylin and eosin stain, ×64.

Some investigators[11, 31, 97] have provided data indicating that the source of infection did not significantly influence the course of gram-negative bacillemia—no differences in mortality were observed in patients with various portals of entry when the severity of underlying noninfectious disease was taken into consideration by the method of McCabe and Jackson.[57] Other investigators[34, 79, 80] have found differences in mortality of gram-negative bacteremia with reference to the primary site of infection. Neeley and associates[79] found a lower mortality for patients in septic shock with infection arising in the urinary tract than for patients in septic shock caused by multiple intraabdominal abscesses or pneumonitis. Nishijima and colleagues[80] found a significantly higher mortality in patients who had gram-negative bacteremic shock from an enteric source of infection than in patients with a nonenteric primary site of infection.

Other workers[17, 34] have noted the relatively mild clinical course and low mortality in patients who had Bacteroidaceae bacteremia with septic abortion compared with patients with Bacteroidaceae bacteremia from extragenital foci of infection. This is probably attributable, in part, to the therapeutic efficacy of curettage and uterine evacuation in septic abortion.[17]

Recent experiences[64] suggest that septic endovascular lesions are often refractory to medical therapy and may be an important factor in the lethal outcome of cases of gram-negative bacillemia. Further study is needed to determine the influence of various portals of entry and of various lesions on the clinical behavior of gram-negative bacillemia.

BACTEREMIA OF LONG DURATION

Investigators in the preantimicrobial era noted that bacteremia caused by opportunistic gram-negative bacilli was frequently of short duration and rarely lasted for more than 1 or 2 days.[28] In recent years, some investigators[58, 89] have emphasized the rapidly fatal course of gram-negative bacillemia especially in patients with lethal underlying noninfectious diseases. However, most studies of large numbers of cases of gram-negative bacillemia have been conducted retrospectively and duration of bacillemia either has not been determined or has not been reported. Members of our group[63] and Harris and Cobbs[38] recently documented the relatively high incidence of bacteremia of long duration among patients with bacillemia caused by opportunistic gram-negative bacilli. From 16 to 30 per cent of all patients with gram-negative bacillemia observed by the two groups had bacteremia of long duration lasting from 4 to 47 days. The large proportion of cases of bacteremia of long duration may have been influenced in part by factors related to requests for consultation with specialists in infectious diseases.[38] The average duration of bacillemia was 13.8 and 19 days in the two series respectively. Often the bacteremia persisted despite appropriate antimicrobial therapy and many of the patients had septic endovascular lesions. Figure 6 is a graphic representation of the clinical course of a patient who had gram-negative

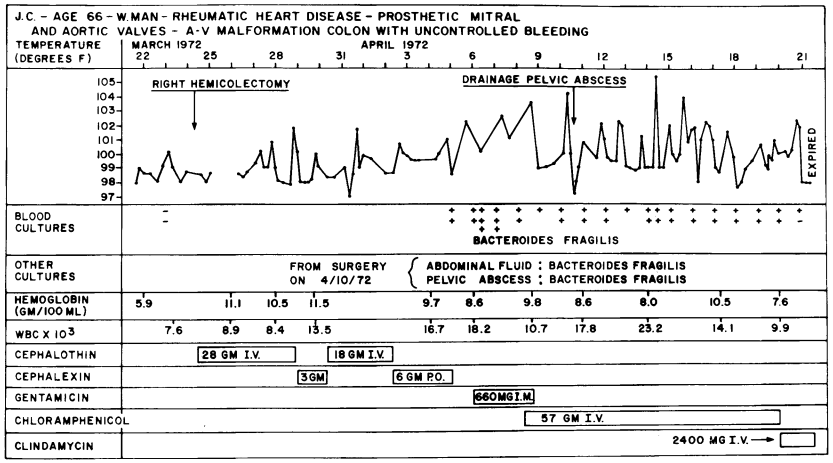

Figure 6. Graphic representation of clinical course of patient with Bacteroides endocarditis proven at autopsy.

bacillary (Bacteroides) endocarditis proved at autopsy. However, it is important to note that many patients with prolonged, gram-negative bacillemia do not have endocarditis. Figure 7 shows the clinical course of such a patient with fibrinopurulent peritonitis; Bacteroides organisms were present in the blood for more than 1 week and there was no evidence of endocarditis at autopsy.

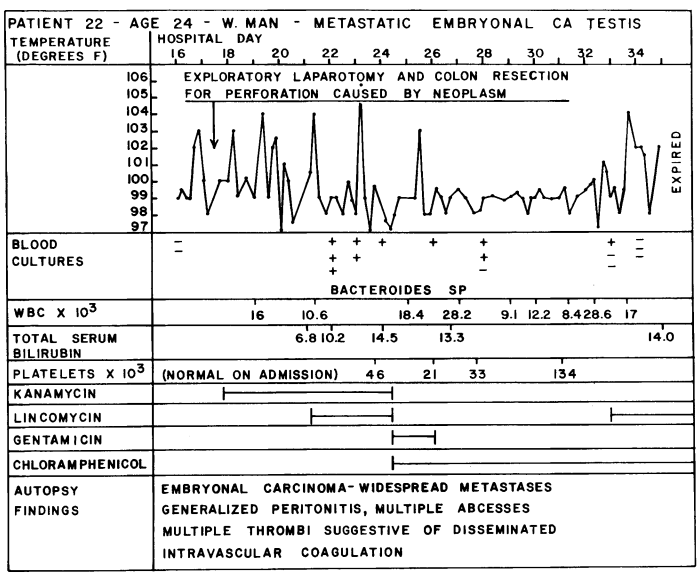

Figure 7. Graphic representation of clinical course of patient with persistent Bacteroides bacteremia secondary to peritonitis without evidence of endocarditis at autopsy.

COMPLICATIONS

In 20 to 30 per cent of patients with gram-negative bacillemia, a clinical syndrome of shock develops and the mortality ranges from 40 to 90 per cent.[60] The pathogenesis of this form of shock is incompletely understood and has been the subject of several recent reviews.[18, 44, 60] Increased attention has been focused on the possible role of immune mechanisms, pharmacologic mediators, vasoactive polypeptides, proteolytic enzymes, and the blood coagulation system.

There is considerable controversy as to whether bacteremic shock is a discrete clinical syndrome with specific hemodynamic defects.[80] Some investigators found that the shock state is associated with a substantial reduction of cardiac output and elevated peripheral vascular resistance.[80] Others[6, 75, 102] observed that septic shock is associated with a high cardiac output and low peripheral vascular resistance. Despite the increased cardiac output, there appears to be defective oxygenation of tissues manifested by elevation of the oxygen content of mixed venous blood, decreased arteriovenous oxygen difference, and lacticacidemia. This defect in oxygenation may result from impaired tissue perfusion secondary to development of arteriovenous shunts which bypass the capillary exchange beds; or it may be caused by inability of the cells of some infected patients to utilize oxygen despite adequate tissue perfusion.

Nishijima and his colleagues[80] postulated that the variability of cardiac output in septic shock reported by various workers reflected the severity of the state of shock at the time the measurements were obtained. They reviewed the data from 159 cases of bacterial shock collected from seven medical centers, including their own, and demonstrated a remarkably high correlation between the initial value of cardiac index and outcome. The survival of patients who had a normal or elevated cardiac output was significantly better than that of patients in whom cardiac output was reduced.

Recent studies indicate that gastrointestinal bleeding[3] and respiratory insufficiency[67, 91] are common complications in patients with bacteremia caused by gram-negative bacilli. The pathogenesis of these complications is incompletely understood, but it is clear that they are important terminal mechanisms of death.[62]

COMMENTS ON MANAGEMENT

Because of its broad range of activity, gentamicin appears to be the drug of first choice for the initial therapy of life-threatening bacteremia caused by aerobic gram-negative bacilli including *E. coli,* Klebsiella-Enterobacter, Serratia, Proteus, and Pseudomonas. However, gentamicin does not achieve high concentrations in bile,[64] and alternative drugs should be used when cholangitis is the source of bacteremia. Gentamicin alone is frequently incapable of curing Pseudomonas bacteremia in patients with severe neutropenia.[7, 41, 64] In this situation, a combination of carbenicillin and gentamicin appears useful; transfusions of granulocytes may also favorably affect the outcome.[37] Clindamycin and chloram-

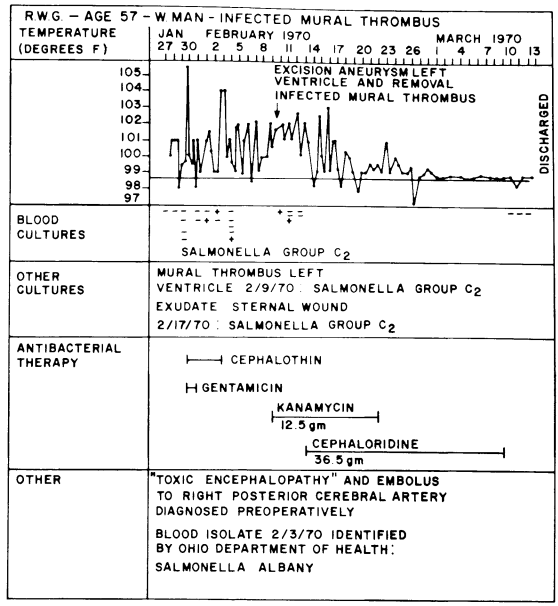

Figure 8. Graphic representation of clinical course of patient with bacteremia secondary to an infected intramural thrombus of the heart.

phenicol appear to be the drugs of first choice for treating bacteremia caused by Bacteroidaceae. The clinical pharmacology of various drugs effective against gram-negative bacilli will be given in more detail in other papers in this symposium.

It is extremely important to search for the source of bacteremia. In some instances, eradication of bacteremia depends upon removal of contaminated intravenous devices, extirpation of suppurative endovascular lesions, drainage of abscesses, or relief of visceral obstruction. Figure 8 is a graphic representation of the clinical course of a patient who required removal of an infected intramural thrombus of the heart for cure of a bacteremic infection caused by *Salmonella albany*.

In evaluating the efficacy of antimicrobial drugs for bacteremia caused by gram-negative bacilli, it is very important to obtain blood cultures immediately before initiation of antimicrobial therapy. Blood cultures may become sterile before the antibiotic is given and eradication of bacteremia may be attributed erroneously to the antibiotic. Figure 9 is a graphic representation of the clinical course of a patient with bacteremia caused by *S. marcescens* 04:H12 secondary to mediastinitis and a postoperative sternal wound infection. Bacteremia subsided after surgical debridement of the wound and before gentamicin therapy was initiated. Failure to obtain pretreatment blood cultures in this patient would have forfeited the chance to recognize this phenomenon. Continuation of gentamicin therapy after bacteremia was required for the wound and mediastinal infection.

It is equally important to obtain blood cultures repeatedly after initiation of antimicrobial therapy in order to recognize therapeutic failure at a time when the bacteremia is still amenable to medical or surgical treatment. Sometimes blood cultures remain positive even when signs of

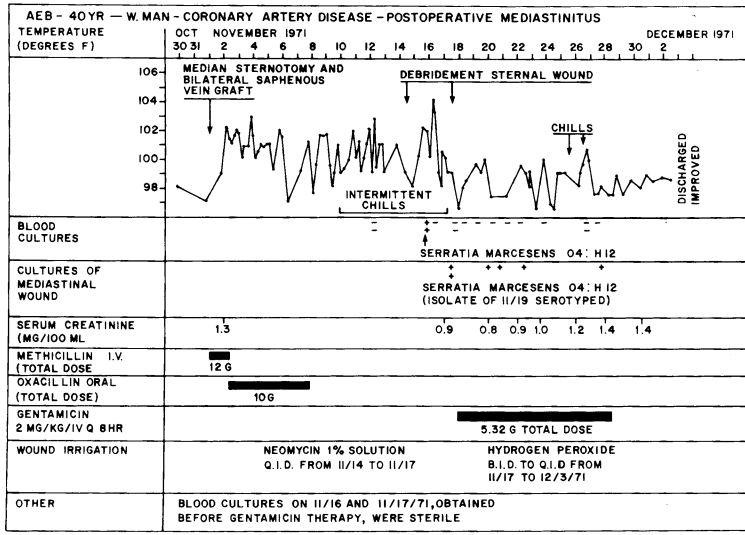

Figure 9. Graphic representation of clinical course of patient in whom bacteremia subsided before gentamicin therapy was initiated.

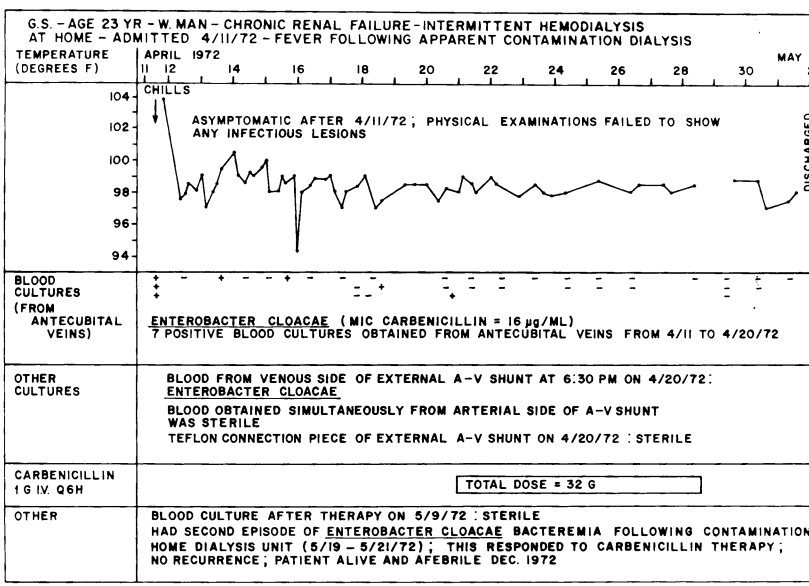

Figure 10. Graphic representation of clinical course of patient who became asymptomatic and afebrile despite persistent bacteremia.

clinical illness have diminished or subsided. Figure 10 shows the clinical course of a bacteremic patient who became afebrile and asymptomatic without therapy; however, bacillemia persisted intermittently until antimicrobial therapy was administered.

In treating patients with bacteremic shock, it is important to remember that hemodynamic derangements may vary among different patients with the same diagnosis or at different times in the same patient.[60] Appropriate therapy depends upon the type of hemodynamic derangement. Blood volume expansion is the keystone of management of the hypovolemic patient with septic shock.[75] Cardiac inotropic agents may be beneficial when shock results from a cardiac defect. The value of adrenal glucocorticoids in the management of bacteremic shock remains controversial.[58, 60, 75, 80, 102]

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The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44106