Gram-negative bacteremia of long duration

Clinical study of 29 patients

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Presented in part at the Eleventh Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Atlantic City, New Jersey, October 19, 1971.

Bacteremia caused by opportunistic gram-negative bacilli frequently is of short duration, varying in severity from transient, self-limiting illness to rapidly lethal disease. In 1924 bacteremia of long duration (BLD) was reported by Felty and Keefer[1] as an uncommon complication of bloodstream infections caused by *Escherichia coli.* They stated that bacteremia rarely lasted more than 1 or 2 days. Since that time, reports of gram-negative bacillus BLD have been limited mostly to single cases,[2-15] to studies of typhoid fever,[16-17] or to investigations of unusual types of salmonellosis.[18-20]

To our knowledge, no systematic study has been undertaken to determine the incidence of BLD in a large number of patients with bloodstream infections caused by *E. coli,* Klebsiella, Enterobacter, *Pseudomonas aeruginosa,* Bacteroides, or other opportunistic gram-negative bacilli. Our investigation was undertaken to detect cases of BLD, to identify the organisms most often involved, and to determine possible pathogenic factors. We are reporting an analysis of our clinical and microbiologic observations and findings in the treatment of 29 patients during 30 episodes

of BLD lasting from 4 to 46 days. In 25 of the 30 episodes, bacteremia persisted for 7 or more days.

Materials and methods

From September 15, 1967, to August 15, 1971, at the Cleveland Clinic Hospital, we examined repeatedly and treated 185 patients with gram-negative bacillus bacteremia; it was of long duration in 29. The criterion for diagnosis of BLD was continuing illness associated with one or more blood cultures positive for the same genus or species of gram-negative bacillus on each of 4 or more days, with a minimum of 4 days between the first and the last positive blood cultures. The duration of bacteremia was measured by the interval between the first and last positive blood cultures for the indicated organism, whether or not any intervening blood cultures were sterile. Recurrences of bloodstream infections in patients who had been asymptomatic and abacteremic for at least 1 week were evaluated independently.

Cultures of blood and infected tissues or body fluids were routinely obtained before, during, and after therapy. For every patient in whom persistent infection was known or even suspected, blood cultures were repeated at intervals of every 1 to 3 days. Samples of the patient's blood obtained under aseptic technique were routinely inoculated into bacteriologic media directly at the patient's bedside. During most of the study, brain-heart infusion broth with polyanetholsulfonate (p.s.s.) anticoagulant and thioglycollate medium with p.s.s. anticoagulant were used. During the last 14 months of the study, the media were casein soy broth with 0.1% agar and 0.05% p.s.s. anticoagulant* and fluid thioglycollate with 0.05% p.s.s. anticoagulant.* All cultures were incubated at 35 to 37 C, examined daily for macroscopic evidence of growth, and were kept 14 days before being considered sterile. Whenever growth appeared in any medium, gram-stained smears and appropriate subcultures were made. During the last 10 months of the study, all blood cultures showing no visible growth after 24 hours of incubation were routinely subcultured on sheep blood agar and chocolate blood agar. The sheep blood agar plates were incubated at 35 to 37 C in an anaerobic jar with a disposable hydrogen generator.† The chocolate blood agar plates were incubated at 35 C in from 8% to 10% carbon dioxide. After 24 hours, all subcultures were examined for evidence of growth and, when indicated, further subcultures were made.

Organisms isolated from blood and other sources of infection were identified by standard bacteriologic techniques.[21] Some isolates were identified only as to genus, but others were identified as to species or a specific serotype. Serotyping of strains of *E. coli,* Klebsiella, and Salmonella was performed at the Center for Disease Control, Atlanta, Georgia, or at the Ohio Department of Health Laboratory, Columbus, Ohio. In some patients, serum bactericidal activity was determined by the method of Schlichter et al;[22] usually the serum specimen was obtained 15 minutes after an intravenous injection of an antibiotic, or 1 or more hours after an intramus-

* *Hyland Laboratories, Costa Mesa, California.*
† *Gas-Pak, Baltimore Biological Laboratories, Baltimore, Maryland.*

cular injection. In vitro susceptibility of bacterial isolates from the blood of patients with BLD was determined either by a macrotube-dilution technique or a microdilution technique described by Gavan and Town.[23] Organisms were considered susceptible to the antibacterial drug (or drugs) administered when their growth was inhibited in vitro by 50 μg/ml or less of carbenicillin; 12.5 μg/ml or less of cephalothin, cephaloridine, cephapirin, chloramphenicol, or kanamycin; 6.3 μg/ml or less of ampicillin or tetracycline; and 3.1 μg/ml or less of gentamicin or polymyxin B.

In fatal cases of BLD, autopsy protocols, histologic sections, and the results of postmortem cultures were reviewed to determine what lesions were related to infection. When indicated, additional microscopic sections were prepared and stained for microorganisms.

Results

During the 47-month period, 29 patients had BLD, 18 men and 11 women, ranging in age from 16 to 73 years. Twenty-eight patients had elevated temperatures (T > 100 F), 18 had shaking chills, and six had periods of systemic arterial hypotension or shock coincidental with the apparent onset of bacteremia. In each of 12 patients, the pathogenesis of bacteremia seemed to be related to a prior surgical procedure on the abdomen, thorax, or lower extremities. Pharmacologic doses of adrenal glucocorticoids were administered during bacteremia in four patients, and both before and during the infection in six patients; in several of the patients, the adrenal glucocorticoids may have ameliorated or masked signs and symptoms of infection. Sixteen patients were in advanced or terminal stages of underlying lethal noninfectious diseases (*Table 1*); they were bedridden, debilitated, cachectic, or comatose; four patients had severe, persistent leukopenia (leukocyte count < 2,000 mm^3) and one had mild leukopenia. Thirteen patients had potentially treatable underlying noninfectious diseases (*Table 1*).

Of the 29 patients, each of 28 had a single episode of BLD, and one patient had two episodes separated by a 3-month interval (*Table 2*). Duration of bacteremia ranged from 4 to 46 days with an average of 13.8 days for the entire group. In most patients, bacteremia was present continuously or intermittently throughout the episode. However, in two patients bacteremia was interrupted by therapy for 1 to 2 weeks; both patients had persistent illnesses, and reseeding of the bloodstream was thought to be caused by a smoldering metastatic focus of infection (i.e., pelvic abscess; subcutaneous inflammatory lesion).

The most common infecting organisms were Klebsiella, *E. coli,* and Enterobacter, followed in order of frequency by Bacteroides, *Pseudomonas aeruginosa,* and miscellaneous bacilli (*Table 2*). Of the 30 episodes, BLD was caused by a single pathogen in 29, and by two organisms in one episode. In one patient, *Pseudomonas* bacteremia was superimposed upon Klebsiella BLD during the last 3 days of the patient's life.

Apparent sources of BLD

The apparent sources of BLD are listed in *Table 3.* In some patients, more than one source of infection may

Table 1. Underlying noninfectious diseases in 29 patients with one or more episodes of BLD

Group	Patients, no.	Deaths, no.
Group I: Advanced or end-stages of incurable noninfectious disease	(16)*	(10)
Metastatic carcinoma (rectum, common bile duct, or testis)	3	1
Acute leukemia, refractory granulocytopenia	3	2
Coma due to inoperable brain tumor or infarct in brain stem	3	2
Inoperable carcinoma (common bile duct or larynx)	2	0
Malignant lymphoma, refractory granulocytopenia	1	1†
Chronic rheumatoid arthritis, aplastic anemia	1	1
Cachexia from perforative Crohn's disease of the colon	1	1
Hepatic cirrhosis, coma, hepatorenal failure, refractory gastrointestinal bleeding	1	1
Coma, hemopneumothorax, lacerated liver, and acute renal failure secondary to trauma	1	1
Group II: Potentially treatable or nonfatal underlying diseases	(13)‡	(3)
Surgical diseases		
Rheumatic or arteriosclerotic heart disease	3	1
Adenocarcinoma (rectum or colon)	2	—
Stricture (common bile duct)	1	—
Arteriosclerotic gangrene in extremity; diabetes mellitus§	1	—
Nonsurgical diseases		
Rheumatic heart disease with functioning aortic valve prosthesis; diabetes mellitus§	1	—‖
Diabetes mellitus; functioning aortoiliac femoral graft	1	1
Diabetes mellitus;§ reversible acute renal failure	1	—
Streptococcus viridans endocarditis with azotemia	1	1
Fever of undetermined etiology (probably blood culture negative bacterial endocarditis)	1	—
Arteriosclerotic heart disease	1	—

* Eight patients received pharmacologic doses ot adrenal glucocorticoids during the infection; four patients with granulocytopenia received cytotoxic chemotherapeutic agents before onset of infection.

† Death caused by superinfection (disseminated candidiasis).

‡ Two nondiabetic patients received pharmacologic doses of adrenal glucocorticoids during the infection.

§ Insulin-dependent diabetes mellitus; mild hyperglycemia during infection.

‖ Outcome undecided at this time.

have been seeding the bloodstream simultaneously or in sequence. Diagnosis was based on clinical or histopathologic evidence of inflammatory disease in an organ, tissue, or biologic fluid other than blood, and by isolation of the indicated pathogen from the appropriate source either antemortem or postmortem, or at both times. There were five exceptions: two patients (three episodes of BLD) with unequivocal clinical evidence of bacterial endocarditis had only positive blood cultures to substantiate the diagnosis. One patient had clinical and roentgenographic evidence of pneumonia and no other apparent nidi of infection, but sputum cultures did not yield the same species of organism as that present in the blood. One patient

Table 2. Causative organisms, number of blood cultures, and duration of bacteremia in 29 patients with BLD

Causative organism(s)	Patients, no.	Blood cultures		Duration of bacteremia, days
		Positive, no.	Total, no.	
Klebsiella*	8	94	105	4–29
E. coli†	6‡	90	163	11–38
Enterobacter	6	77	83	5–46
Bacteroides	4	30	50	11–15
Pseudomonas aeruginosa	2	20	26	9–16
Salmonella albany	1	5	13	11
Providence	1	11	16	9
Bacteroides (10 cultures) and Flavobacterium (11 cultures)	1	21	21	19
Total	29	348	477	4–46
Mean				13.8 days

* Klebsiella type 28 (one patient).
† *E. coli* 075A:75B (one patient), *E. coli* 06:NM (one patient), and *E. coli* 075A:75B:NM (one patient).
‡ One patient with endocarditis had two episodes due to *E. coli*, untypable.

Table 3. Sources of continuing infection in 29 patients with BLD

Apparent source of continuing infection	Patients, no.	Deaths, no.
Endovascular sources	13	7
Suppurative phlebitis portal or iliac veins (associated with peritonitis, hepatic and/or abdominal abscesses)	3	3
Endocarditis* †	3	2
Suppurative phlebitis I. V. cannula site	3	2
Cellulitis I. V. cannula site	2	0
Contaminated I. V. solution	1	0‡
Infected intramural thrombus (left ventricle)	1	0
Suppurative cholangitis	3	0
Mediastinitus	2	0
Pneumonia	2	1
Cellulitis or necrotizing pharyngitis in granulocytopenic patients	2	2
Generalized peritonitis with abscesses	2	1
Pneumonia and contaminated I. V. cannula	2	1
Crepitant cellulitis at amputation site	1	0
Pelvic abscess	1	0
Indeterminant	1	0
Total	29	12‡

* Endocarditis developed as an apparent complication of a contaminated intravenous solution, one patient.
† Two episodes of BLD (*E. coli*) in one patient; the valvular infection developed from bacteremia caused by acute pyelonephritis.
‡ In one patient bacteremia was eradicated, but death was caused by systemic candidiasis.

had no apparent clinical evidence of inflammatory lesions; however, cultures of an indwelling intravenous cannula and intravenous solution revealed the same organism as that present in the blood cultures. Postmortem cultures of hepatic and abdominal abscesses in the fifth patient yielded aerobic gram-negative bacilli, but not Bacteroides, which caused the BLD. In this instance, the absence of growth of Bacteroides from postmortem specimens might be due to our failure, in the presence of a polymicrobic flora, to use media selective for Bacteroides.

The most frequent sources of BLD were intravascular foci, such as infections proved by cultures at sites of intravenous cannulas, with visible cellulitis or microscopically demonstrable suppurative thrombophlebitis; endocarditis or infected intracardiac thrombus; suppurative thrombophlebitis of portal or iliac veins; and a contaminated intravenous solution, with no other recognizable source of infection (one patient). These sources accounted for 14 episodes of BLD in 13 patients, and for 7 of the 12 deaths attributed to bacterial infection. In two additional patients with pneumonia, contaminated intravenous cannulas may have been involved in persistence of bacteremia. Of the seven patients in each of whom an intravenous cannula appeared to be a primary or a possible secondary source of BLD, intravenous solutions were not cultured in six (because the possibility of contamination was not considered), and were sterile in one patient. Furthermore, in one patient with an undetermined portal of entry for BLD, cultures of intravenous solutions and the intravenous cannula were not obtained, but when intravenous therapy was discontinued, Enterobacter bacteremia promptly subsided. Thus, it is possible that undetected contaminated intravenous solutions may have been the source of bacteremia in the patient with an undetermined portal of infection and in some of the patients in whom infection was attributed to intravenous cannulas. Contamination of intravenous fluids was proved in two cases in this study: in one patient, fatal Enterobacter endocarditis developed, and the other patient had refractory Providence bacteremia that subsequently responded to therapy after the use of the contaminated intravenous apparatus was discontinued.

Miscellaneous sources of 13 episodes of BLD in 13 patients included cholangitis, mediastinitis, necrotizing cellulitis or pharyngitis in granulocytopenic patients, pneumonia, peritonitis, pelvic abscess, and crepitant cellulitis at an amputation site in the lower extremity. Of the 29 patients in this study, only three had clinical or autopsy evidence of acute pyelonephritis; all three had extrarenal lesions that caused BLD.

Results of therapy of BLD

All of the patients with BLD received antibacterial medication. In 1 of the 29 patients, who had Enterobacter endocarditis, the causative organism was resistant in vitro to all antibiotics tested; various antibacterial regimens were ineffective, surgery was not attempted, and the patient died. In 6 of the 29 patients, a delay of 3 or more days occurred before appropriate therapy was started. Either the significance of initial positive blood cultures was not immediately appreciated (because of the indolent nature of the illness produced by bacteremia)

or ineffective antibiotics were administered preceding tests of in vitro susceptibility. Four of the six patients recovered after appropriate therapy was administered. In 1 of the 29 patients, discontinuance of chloramphenicol therapy after an afebrile, abacteremic period of 3 days was followed unexpectedly by recurrence of Bacteroides bacteremia; a second course of therapy was curative.

In 21 patients, bacteremia persisted for 3 or more days despite parenteral administration of one or more antibiotics shown to be effective in vitro against the organisms causing bacteremia. *Figures 1 and 2* are graphic representations of the clinical courses of two of those patients. Eighteen of the 21 patients received kanamycin or gentamicin, either alone (six patients); or with a cephalosporin (eight patients), chloramphenicol (two patients), carbenicillin (one patient), or a tetracycline (one patient). Multiple antibiotics were administered in sequence in a number of these patients. Of the 21 patients, serum bactericidal tests were performed in nine; in eight serum bactericidal activity was present in a titer of 1:32 or less. In 12 of the 21 patients, bacterial infection eventually was eradicated; in most instances, recovery was hastened by removal of intravenous devices, by surgical excision or drainage of nidi of infection, or by spontaneous drainage of suppurative lesions.

Of the 29 patients with BLD, 13 died as a result of infection. Major factors contributing to the deaths were severe underlying noninfectious diseases, septic intravascular lesions, undrained abscesses, persistent granulocytopenia, and disseminated intravascular coagulation (one patient). In 1 of the 13 patients, bacterial infection was eradicated, but death was caused by systemic candidiasis. At present, for 1 of the 29 patients, the outcome is still in doubt. She has *E. coli* endocarditis involving a prosthetic aortic valve; a third episode of *E. coli* bacteremia (which did not meet the criterion for BLD) was recently treated; whether the patient can be maintained

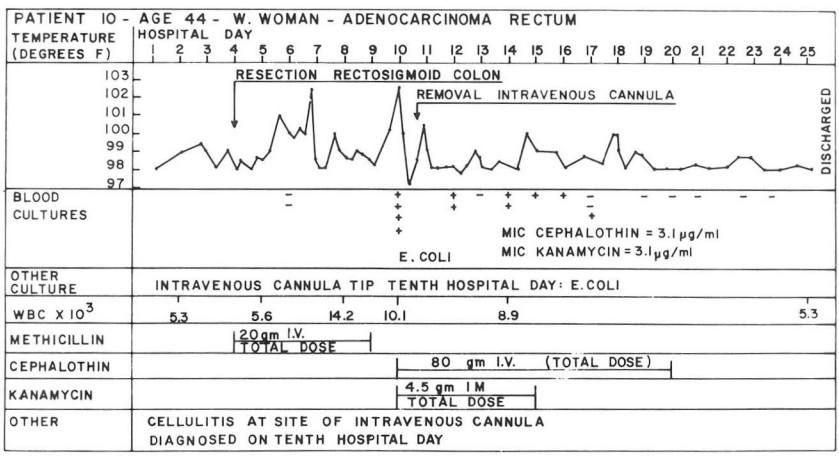

Fig. 1. Course of a patient with BLD caused by *E. coli* with underlying cellulitis at site of indwelling intravenous cannula. Bacteremia persisted for several days despite the removal of the intravenous device and the use of appropriate antibacterial therapy.

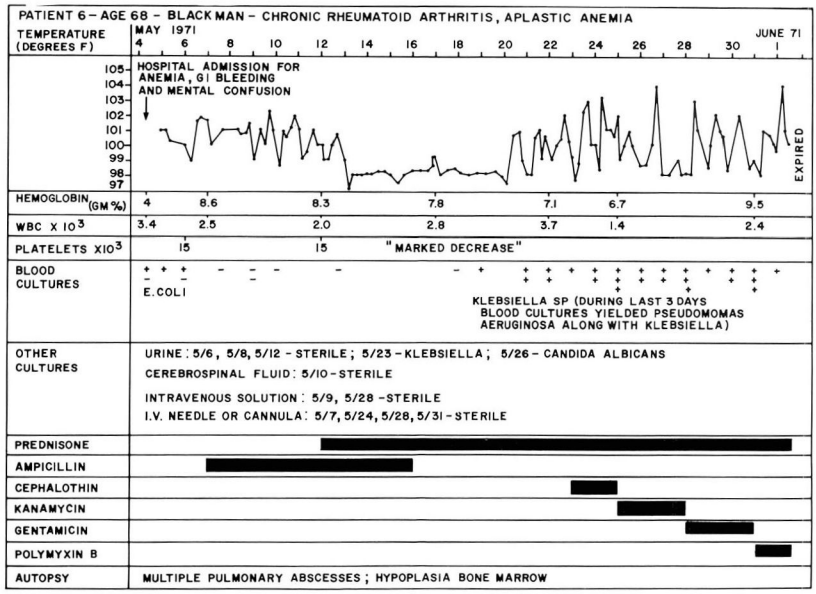

Fig. 2. Course of a patient with BLD caused by Klebsiella. Bacteremia persisted despite therapy with several antimicrobials to which the causative organisms were shown to be susceptible in vitro. Pseudomonas bacteremia was superimposed upon Klebsiella bacteremia during the last 3 days of the patient's life.

on long-term suppressive antimicrobial therapy without surgical replacement of the infected prosthetic valve is in question.

Discussion

Results of our study show that a surprisingly large number of patients with bacteremia produced by opportunistic gram-negative bacilli have those organisms in their bloodstream intermittently or persistently for long periods ranging from several days to several weeks. The high incidence of BLD (16% of 185 patients) was not caused by a single bacterial species or a single pathogenic mechanism. In most instances, bacteremia persisted despite what appeared to be appropriate antibiotic therapy. Delayed or absent response to specific antibiotics was associated with septic endovascular lesions, intravascular foreign bodies, undrained abdominal, hepatic, or mediastinal abscesses, spreading cellulitis of loose areolar tissues, necrotizing bacillary lesions in granulocytopenic patients, or suppurative lesions in obstructive viscera.

In our patients with BLD, apparent sources of continuing infection were invariably outside the urinary tract, in contradistinction to those in the majority of cases of bacteremia caused by opportunistic gram-negative bacilli. In some instances persistence of bacteremia despite eradication of bacteriuria directed attention to the presence of extraurinary lesions. Other investigators[13] have reported isolated cases of prolonged gram-negative bacillus bacteremia produced by obstructive pyelonephritis.

If repeated blood cultures are ob-

tained from patients with gram-negative bacillemia, BLD may be encountered more frequently. There are indications that this may be true. For example, Finland and Barnes[24] at the Boston City Hospital noted a marked increase in the incidence of fatal endocarditis caused by gram-negative bacilli. Likewise, there now seems to be a larger number of bloodstream infections produced by those organisms as apparent contaminants of intravenous catheters or solutions.[25-27] BLD may occur when those sources of infection are not extirpated promptly. Unfortunately, tardy diagnosis and removal of those devices is a hazard because local signs and symptoms of infection are often absent, subtle, delayed in their onset, or overlooked. Thirty years ago, Keefer[28] stressed that bacteremia due to common pyogenic organisms, without local signs of infection, should arouse suspicion of an intravascular focus such as infected thrombophlebitis or endocarditis. Recent studies[29, 30] attest to the role of septic vascular lesions in fatal cases of bacteremia caused by gram-negative bacilli.

We believe that clinicians should be aware that an appreciable number of patients with bacteremia caused by opportunistic gram-negative bacilli may have protracted illnesses of several days to several weeks. Long duration of bloodstream infection causes difficulties in diagnosis, problems in management, protracted morbidity, prolonged exposure of victims to the hazards of antimicrobials, and high mortality. Specific antimicrobial therapy often has limited success in cases of BLD and, therefore, efforts must be directed toward locating, draining, or extirpating distributing foci of infection, and correcting other predisposing factors such as granulocytopenia or obstruction of viscera. The remarkable ability of some patients to survive bacteremia for long periods provides an opportunity for definitive therapy.

Summary

A total of 185 consecutive patients were treated for gram-negative bacteremia; 29 had gram-negative bacillary bacteremia of long duration (BLD). One or more blood cultures were positive for the same genus or species of gram-negative bacillus on each of 4 or more days during a continuing illness. Bacteremia lasted from 4 to 46 days. The most frequent pathogens were Klebsiella, *Escherichia coli*, Enterobacter, and Bacteroides. Sources of infection included septic endovascular lesions, intravascular foreign bodies, abdominal or hepatic abscesses, peritonitis, cholangitis, mediastinitus, pneumonia, cellulitis, and necrotizing lesions in granulocytopenic patients. In most patients, BLD occurred despite appropriate systemic antibiotic therapy, and additional measures were required for cure. Sixteen patients survived, 13 died. This study indicates that BLD is a frequent, serious complication of bloodstream infections caused by opportunistic gram-negative bacilli.

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