Gram-negative bacteremia: variable clinical course and useful prognostic factors

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In recent years, bacteremia caused by gram-negative bacilli has become a common cause of death. It is estimated that from 18,000 to 100,000 deaths are now caused by gram-negative bacteremia in the United States each year.[1, 2] Coexistent diseases[3-9] and shock[10] appear to be major determinants of outcome. However, in most published studies of gram-negative bacteremia, deaths caused by infections have not been differentiated from those unrelated to infection,[1] the effect of duration of bacteremia on outcome has not been assessed[11-13] and, to our knowledge, no attempt to grade the illness produced by infection has been reported. Furthermore, opinions vary concerning the possible relationship of the apparent portal of entry of the causal organism to outcome. Some investigators[8, 14, 15] found a significantly higher mortality from gram-negative bacteremia when it arose from the abdomen or lung than when it developed from the urinary tract or pelvic cavity. However, other investigators[4-6] found that the source of bacteremia did not significantly influence mortality when the grade of underlying disease was taken into consideration.

The investigation we report here was undertaken in order to study the course of gram-negative bacteremia and to assess the possible influence of the following five factors on the outcome of the infection: (1) duration of the episode of

bacteremia, (2) grade of systemic illness attributed to the infection, (3) apparent portal of entry of the causal organism, (4) grade of the underlying disease, and (5) antimicrobial chemotherapy. Each patient included in this study had one or more blood cultures positive for gram-negative bacilli and was examined by one or more of the authors. Patients whose positive blood cultures were caused by, or even were suspected of being due to spurious contamination were excluded from the study.

Materials and methods

During a 5-year period from September 15, 1967 to September 15, 1972, at the Cleveland Clinic Hospital, 257 patients were treated by one or more of the authors for 285 episodes of bacteremia caused by gram-negative bacilli as proved by blood cultures. There were 162 males and 95 females ranging in age from 1 to 89 years; the average age was 52.3 years.

For each patient the medical history was reviewed, physical examination was performed, and appropriate laboratory studies were obtained. Signs and symptoms of local infection and systemic illness were diagnosed whenever possible. Cultures of the blood were obtained routinely before, during, and after therapy. When persistent infection was known to be present, or even suspected clinically, blood cultures were performed repeatedly at 1- to 3-day intervals. Whenever possible, Gram-stained smears and cultures of exudates, abscesses, or infected body fluids were obtained before initiation or change of antimicrobial therapy. In all cases, when necessary, appropriate measures were taken to eradicate infection, to restore adequate tissue perfusion,[16] to control underlying disease, and to treat any complications.

Blood cultures. Samples of each patient's blood were obtained under aseptic technique and routinely inoculated into bacteriologic media at the patient's bedside. In most instances, times that the blood cultures were obtained were recorded. During the first 33 months of this study, brain-heart infusion broth with sodium polyanetholsulfonate (SPS) anticoagulant and thioglycollate medium with SPS anticoagulant were used. During the last 27 months of the study, casein soy broth with 0.1% agar and 0.5% SPS anticoagulant (Hyland Laboratories) and fluid thioglycollate medium with 0.5% SPS anticoagulant (Hyland Laboratories) were employed. All cultures were incubated at 35 to 37 C, examined daily for macroscopic evidence of growth, and kept at least 14 days before being considered sterile. Whenever growth appeared in any medium, Gram-stained smears and appropriate subcultures were made. During the last 23 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 (Gas-Pak, Baltimore Biological Laboratories). The chocolate blood agar plates were incubated at 35 C in 8% to 10% carbon dioxide. All subcultures were examined after 24 hours for evidence of growth, and further subcultures were done when indicated.

Pathogens. Organisms isolated from the blood and other sites of infection were identified by conventional bacteriologic techniques.[17] Some isolates

were identified only as to genus, most were speciated, and some were identified as to a specific serotype, capsular type, or pyocin type. Strains of *Escherichia coli,* Klebsiella, Serratia, Salmonella, and *Pseudomonas aeruginosa* were typed at the Center for Disease Control, Atlanta, Georgia, or at the Ohio Department of Health Laboratory, Columbus, Ohio. For the last 52 months of the study, in vitro susceptibility of rapidly growing aerobic bacterial isolates was tested routinely by means of the standardized single-disk techniques of Bauer et al.[18] (For the first 8 months, a modification of this method was used.) For most blood isolates, susceptibility also was tested by a macrotube-dilution technique or by microdilution techniques;[19, 20] our criteria for tube dilution susceptibility have been reported.[12] For anaerobic bacilli, antimicrobial susceptibility was tested by an agar disk technique with sheep blood agar plates incubated anaerobically; standardized interpretive criteria for this test are not yet available. In some instances, disk-test susceptibility of anaerobic blood isolates was supplemented by tube-dilution susceptibility tests.

Illness caused by infection. Patients were considered to have definite systemic illness caused by infection when at least three of the following signs or symptoms were present that could not be attributed reasonably to causes other than infection: shaking chills, fever (temperature of at least 102 F rectal or 101 F oral), tachypnea (respiratory rate of at least 24/min), tachycardia (pulse rate of at least 110/min), leukocytoses (>11,000 leukocytes/mm^3) or leukopenia (<3,000 leukocytes/mm^3). The following conditions were considered to be complications of infection when they could not be attributed reasonably to factors other than the infection: significant systemic arterial hypotension or overt shock, mental confusion, delirium or coma, azotemia, jaundice, metabolic acidosis, respiratory insufficiency, metastatic abscesses, hypothermia, or disseminated intravascular coagulation with hemorrhage. The grade of illness attributed to infection was classified into one of three categories: (1) *Mild*—uncomplicated infection and minimal systemic illness; (2) *Moderate*—uncomplicated infection and definite systemic illness; (3) *Severe*—complicated illness caused by infection.

Duration of bacteremia. This was determined as the interval between the first and last positive blood cultures for the same genus, species, or serotype of bacteria during a continuing illness, whether or not any intervening blood cultures were sterile. Recurrences of bacteremia in patients who had been afebrile and abacteremic for at least one week after the last positive blood culture were evaluated independently. For each bacteremic episode, duration was classified into one of three categories based on a modification of the method of Harris and Cobbs:[13] transient, persistent, or indeterminate. Transient bacteremia is comprised of episodes that lasted less than 7 days. Persistent bacteremia is comprised of episodes that lasted 7 days or more. Indeterminate bacteremia is comprised of episodes, the duration of which could not be assessed adequately because of insufficient numbers of blood cultures or of uncertainty as to timing.

Classification of patients. Patients were classified into two broad groups according to the grade of the underlying disease(s) based on a modifica-

tion of the McCabe-Jackson method[3] which we used previously.[11] Group I comprised those patients who were considered to be in advanced or terminal stages of incurable medical or surgical diseases. These patients had illnesses estimated to be either rapidly fatal (within 30 days) or ultimately fatal (within 4 years) by the McCabe-Jackson method.[3] The classification was based upon the observation of the grade of the underlying illness of the patient rather than upon the specific diagnosis. Most of the patients in Group I were bedridden, debilitated, malnourished or cachectic, or comatose from the underlying disease.

In Group I patients, some of the conditions responsible for the illness were metastatic carcinoma; acute leukemia with persistent profound granulocytopenia or intractable blastic crises; refractory malignant lymphoma; multiple myeloma with severe renal failure; prolonged coma due to brain tumor or massive infarct; leaking or ruptured abdominal aortic aneurysm requiring immediate surgical intervention, complicated by intractable renal failure or gangrene of the colon; severe chronic rejection of renal transplant with cachexia; end-stage hepatic cirrhosis; transmural colitis with cachexia; end-stage renal disease without benefit of dialysis.

Group II comprised those patients (none of whom were cachectic) who had potentially treatable or nonfatal underlying diseases, such as medical or surgical diseases of the gastrointestinal, genitourinary or biliary tracts, skeletal or cardiovascular system, or diabetes mellitus. Four well-nourished patients with chronic renal failure required intermittent hemodialysis; otherwise, none of the patients in Group II had evidence of severe organ failure before the apparent onset of the infection.

Classification of antimicrobial chemotherapy. Based on in vitro studies, antimicrobial chemotherapy* was classified into one of three categories: appropriate, inappropriate, or indeterminate. The appropriate category comprised therapy by an appropriate route of therapeutic doses of one or more antimicrobial drugs to which the infecting organism was shown to be susceptible. The inappropriate category comprised treatment with antimicrobial drugs *only* to which the infecting organism was resistant in vitro. This usually occurred because cultural information was not available at the time therapy was started. The indeterminate category comprised therapy administered to those patients in whom susceptibility testing of blood isolates was not performed by a routine standardized disk or dilution technique. Five patients received no antimicrobial chemotherapy.

Classification of outcome of infection. The outcome of the infection was classified as follows: recovery—survival and disappearance of all signs and symptoms of acute infection with sterile blood cultures during and after therapy; death—caused by or associated with persistent acute infection or suprainfection, whether or not bacteremia had terminated before death. Death from causes clearly unrelated to persistent acute infection or suprainfection were excluded from the fatal category.

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* *The antibacterial drugs administered (either alone or in various combinations) were: ampicillin, carbenicillin, a cephalosporin, chloramphenicol, gentamicin, kanamycin, lincomycin, a polymyxin, a tetracycline.*

Autopsy studies. All protocols of autopsies, histologic sections, and the results of postmortem cultures were reviewed in order to correlate lesions with infection. When indicated, additional microscopic sections with appropriate stains for microorganisms were obtained.

Statistical significance. The chi square test was used to determine statistical significance when more than five values were present in all categories. When less than five values were present in any one category, Fisher's exact test was employed.

Results

Organisms responsible for the 285 episodes of bacteremia in the 257 patients are listed in *Table 1*. Single pathogens were responsible for 253 episodes and two or more organisms were isolated from the blood during each of 32 episodes. Of the 257 patients, 236 each had a single episode and 21 patients each had two or more episodes. Twelve patients each had two or more episodes of bacteremia caused by different species of gram-negative bacilli, and nine patients each had recurrent episodes caused by the same species or serotype of organisms.

E. coli was the single pathogen most frequently involved in monomicrobial and polymicrobial bacteremia. However, when taken as a group, members of the division Klebsiella-Enterobacter-Serratia were the most frequent cause of bacteremia in this study. Members of the family Bacteroidaceae were the third most common cause of bacteremia, followed in order of frequency by *P. aeruginosa, Proteus mirabilis,* and miscellaneous organisms. There was no significant difference in mortality from infection for the various pathogens when grade of underlying disease and grade of illness attributed to infection were taken into consideration.

The outcome of infection was fatal in 89 (31.2%) of the 285 episodes (*Table 1*). The relationship of outcome of infection to the grade of underlying disease and to the grade of illness attributed to the infection is shown in *Table 2*. For each of the three grades of illness attributed to infection, mortality was significantly higher in patients with advanced or terminal stages of incurable underlying diseases than in those patients with potentially treatable or nonfatal underlying diseases ($p < 0.02$). For each of the two categories of underlying diseases, the mortality was highest for patients with severe illness attributed to infection, was intermediate for those with moderate illness, and was lowest for those with mild illness. However, the differences were statistically significant only when the groups with severe illness attributed to infection were compared to those with moderate or mild illness or both ($p < 0.02$). There was no correlation between age and sex of patients and outcome of infection when the grade of underlying disease and the grade of illness due to infection were taken into consideration.

Of the 285 episodes of bacteremia, duration was transient (less than 7 days) in 216 (75.8%), persistent (7 to 46 days) in 46 (16.1%) and indeterminant in 23 (8.1%). The overall effect of persistent bacteremia was to increase fatality (*Table 3, Fig. 1*). A significantly higher mortality was associated with persistent bacteremia than with transient bacteremia in two large subgroups of patients: (1) those pa-

Table 1. Relationship of organism responsible for bacteremia and outcome of infection

Organism(s) responsible for bacteremia	Outcome of infection	Grade of illness attributed to infection						No. of episodes	Fatality %
		Severe		Moderate		Mild			
		Gr I*	Gr II*	Gr I*	Gr II*	Gr I*	Gr II*		
E. coli	Recovery	2	11	9	21	2	5	50	26.4
	Death	7	3	6	—	2	—	18	
Klebsiella sp	Recovery	4	9	12	9	—	4	38	26.9
	Death	9	—	3	2	—	—	14	
Bacteroides sp†	Recovery	—	8	4	7	—	6	25	35.9
	Death	7	4	2	—	1	—	14	
Enterobacter sp‡	Recovery	5	3	4	15	—	3	30	14.3
	Death	—	—	4	1	—	—	5	
Pseudomonas aeruginosa	Recovery	1	4	5	2	2	1	15	48.3
	Death	10	2	2	—	—	—	14	
Proteus mirabilis	Recovery	—	2	2	—	2	2	8	27.3
	Death	1	—	2	—	—	—	3	
Serratia marcescens	Recovery	—	—	1	3	—	2	6	25.0
	Death	1	1	—	—	—	—	2	
Herellea vaginicola	Recovery	—	2	—	—	—	1	3	25.0
	Death	—	—	1	—	—	—	1	
Salmonella sp§	Recovery	1	1	—	—	—	—	2	33.3
	Death	—	1	—	—	—	—	1	
H. influenzae	Recovery	—	—	—	1	—	—	1	50.0
	Death	—	—	1	—	—	—	1	
Providence sp	Recovery	—	—	—	—	—	—	—	100.0
	Death	—	—	1	—	—	—	1	
Unidentified gram-negative bacillus	Recovery	—	—	—	1	—	—	1	—
	Death	—	—	—	—	—	—	—	
Polymicrobic etiology‖	Recovery	2	4	3	5	3	—	17	46.9
	Death	10	3	2	—	—	—	15	
Total	Recovery	15	44	40	64	9	24	196	31.2
	Death	45	14	24	3	3	—	89	

* Group I—advanced or terminal stages of incurable underlying diseases; Group II—potentially treatable or nonfatal underlying diseases.

† *Bacteroides fragilis* (15); not speciated (24).

‡ *Enterobacter* sp (24); *cloacae* (6); *aerogenes* (3); *liquefaciens* (1); *agglomerans* (1).

Table 1.—*continued*

§ *Salmonella typhimurium* (1); *albany* (1); *newport* (1).
‖ *E. coli* and *Klebsiella* sp (4); *E. coli* and Enterococcus (2); *E. coli* and *Pseudomonas aeruginosa* (2); *Bacteroides* sp and Enterococcus (2); *Enterobacter* sp and *E. coli* (2); *Aeromonas* sp and *Clostridium perfringens* (1); *Proteus mirabilis* and *Proteus rettgeri* (1); *Proteus mirabilis* and *Pseudomonas aeruginosa* (1); *E. coli 04:H5, Candida tropicalis* and *Bacteroides* sp (1); *Proteus mirabilis, Citrobacter freundi, E. coli, Klebsiella* sp and Enterococcus (1); *E. coli* and *Staphylococcus epidermidis* (1); *E. coli, Proteus mirabilis* and *Pseudomonas aeruginosa* (1); *E. coli*, Enterococcus and *Enterobacter* sp (1); *E. coli* and *Clostridium sporogenes* (1); *Klebsiella* sp and *Aeromonas hydrophilia* (1); *Klebsiella* sp and *Pseudomonas aeruginosa* (1); *Bacteroides* sp and *Staphylococcus aureus* (1); *Bacteroides fragilis, E. coli 05:NM, Klebsiella Type 8* and *Proteus mirabilis* (1); *Bacteroides* sp and *Proteus rettgeri* (1); *Bacteroides* sp and *Flavobacterium* sp (1); *Enterobacter* sp and *Klebsiella* sp (1); *Enterobacter* sp and *Bacteroides* sp (1); *Pseudomonas aeruginosa* and Enterococcus (1); *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* (1); *Pseudomonas aeruginosa* and Group A beta hemolytic streptococcus (1).

tients with potentially treatable or nonfatal underlying diseases (Group II) who had severe illnesses caused by infection ($p < 0.004$), and (2) those patients who were in advanced or terminal stages of underlying incurable diseases (Group I) and who had moderate illness attributed to infection ($p < 0.05$). Contrary to expectation, mortality among Group I patients with severe illness and transient bacteremia was not significantly different from that of Group I patients with severe illness and persistent bacteremia. Duration of bacteremia could not be demonstrated to contribute significantly to the mortality among Group II patients with moderate illness or in patients with mild illness, regardless of the grade of underlying disease. However, the small number of patients in the latter category makes it difficult to assess the statistical significance of differences noted.

Bacteremia arose from a wide variety of portals of entry (*Table 4*). However, in 70% of the episodes the apparent portal of entry was one of the following: the urinary tract (18.9%), contaminated intravenous devices (15.4%), intraabdominal cavity (15.1%), respiratory tract (10.8%), or

Table 2. Correlation of outcome of infection to grade of systemic illness attributed to infection and the grade of the underlying disease

Group and outcome	Grade of systemic illness attributed to infection No. of episodes (%)		
	Severe	Moderate	Mild
I (Advanced or terminal stages of incurable underlying disease)	60	64	12
Recovery	15 (25%)	40 (62.5%)	9 (75%)
Death	45 (75%)	24 (37.5%)	3 (25%)
II (Potentially treatable or nonfatal underlying disease)	58	67	24
Recovery	44 (75.86%)	64 (95.52%)	24 (100%)
Death	14 (24.14%)	3 (4.48%)	0 (0%)

Table 3. Correlation of outcome of infection, grade of illness attributed to infection, extent of underlying disease and duration of bacteremia in 234 patients with 262 episodes*†

Group and outcome	Grade of illness attributed to infection, no. of episodes of bacteremia						
	Severe		Moderate		Mild		Total
	<7 days	≥7 days	<7 days	≥7days	<7 days	≥7 days	
I (Advanced or terminal stages of incurable underlying diseases)	54		62		11		127
Recovery	10	3	35	4	8	0	60
Death (%)	30 (75%)	11 (78.6%)	16 (31.4%)	7 (63.6%)	2 (20.0%)	1	67 (52.8%)
Total	40	14	51	11	10	1	
II (Potentially treatable or nonfatal underlying diseases)	54		59		22		135
Recovery	35	5	51	5	20	2	118
Death (%)	7 (16.7%)	7 (58.3%)	2 (3.8%)	1 (16.7%)	0 (0%)	0	17 (12.6%)
Total	42	12	53	6	20	2	

* In an additional 23 patients, duration of 23 episodes of bacteremia was indeterminate.

† Duration of the 46 episodes of persistent bacteremia ranged from 7 to 46 days.

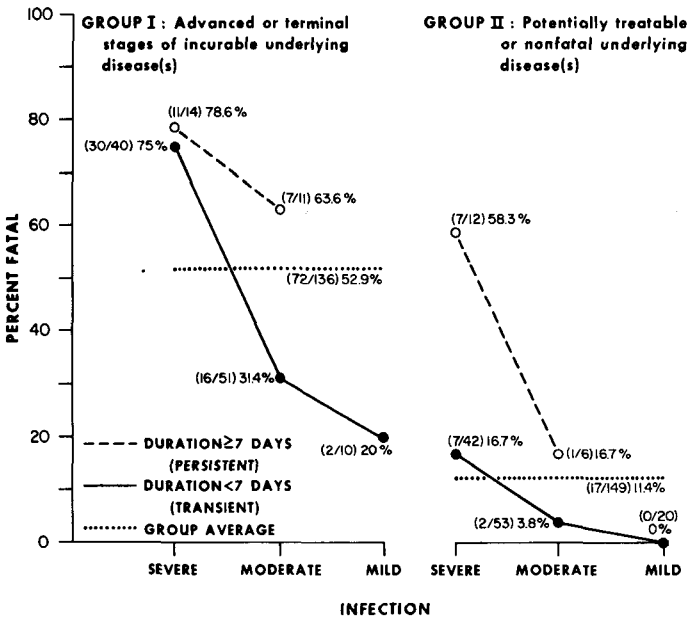

Fig. 1. Graph represents the percentage of fatality of infection related to episodes of gram-negative bacteremia by groups of underlying disease, grades of illness attributed to infection, and duration of bacteremia. The mild classification for persistent bacteremia (≥ 7 days) is not included because of the small number of cases.

pelvic cavity (9.8%). The portal of entry was undetermined in 9.5%.

The relationship of the apparent portal of entry for bacteremia to outcome of infection is shown in *Table 4*. The results are classified according to the grade of illness attributed to infection and to the grade of underlying disease. *Figure 2* is a graphic representation of the relationship of incidence of mortality to the grade of underlying disease, to the grade of illness attributed to infection, and to the five most common portals of entry of bacteremia. For purposes of presentation in this graph, data of mild and moderate illness due to infection were combined into a single category designated as nonsevere illness. In patients with potentially treatable or nonfatal underlying diseases (Group II), when the portal of entry was the respiratory tract, pelvis, urinary tract, or contaminated intravenous devices, the incidence of mortality was 7.07%, regardless of the grade of illness due to infection. In contrast, intraabdominal infections had no mortality in patients with nonsevere illness and potentially treatable or nonfatal underlying diseases (Group II). However, when the grade of illness due to infection in Group II patients was severe, the mortality for intraabdominal infections was 54.6% ($p < 0.06$). Grade of illness due to infection had a similar influence on mortality from intraabdominal infections in patients in advanced or terminal stages of incurable diseases (Group I).

Pelvic infections had the lowest overall mortality and fared similarly with appropriate management, regardless of the grade of underlying disease

Table 4. Correlation of apparent portal of entry of bacteremia and outcome of infection

Apparent portal of bacteremia	Outcome of infection	Grade of illness attributed to infection: Severe Gr I*	Severe Gr II*	Moderate Gr I*	Moderate Gr II*	Mild Gr I*	Mild Gr II*	No. of episodes	Fatality %
Urinary tract	Recovery	3	4	13	18	3	4	45	16.6
	Death	6	0	2	0	1	0	9	
Intravenous devices†	Recovery	3	9	4	15	1	6	38	13.6
	Death	1	0	3	2	0	0	6	
Abdomen‡	Recovery	3	5	6	3	0	2	19	55.8
	Death	15	6	3	0	0	0	24	
Respiratory tract§	Recovery	1	7	3	3	0	1	15	51.6
	Death	11	2	3	0	0	0	16	
Pelvis‖	Recovery	2	7	7	3	3	3	25	10.7
	Death	0	2	1	0	0	0	3	
Wound infections**	Recovery	0	3	0	8	0	3	14	26.3
	Death	1	2	2	0	0	0	5	
Biliary tract††	Recovery	2	3	0	3	0	1	9	25.0
	Death	1	0	2	0	0	0	3	
Necrotizing agranulocytic lesions‡‡	Recovery	1	1	1	0	1	0	4	66.7
	Death	4	0	4	0	0	0	8	
Endocarditis, infected mural thrombus or aneurysm	Recovery	0	1	1	2	0	1	5	44.4
	Death	1	2	0	1	0	0	4	
Miscellaneous§§	Recovery	0	1	0	2	0	0	3	50.0
	Death	1	0	0	0	2	0	3	
Indeterminate	Recovery	0	3	5	7	1	3	19	29.6
	Death	4	0	4	0	0	0	8	

* Group I—advanced or terminal stages of incurable underlying diseases; Group II—potentially treatable or nonfatal underlying diseases.

† Intravenous cannulas (32); intravenous solutions (9); arteriovenous shunt (3).

‡ Generalized peritonitis (25); intraabdominal abscesses (17); fatal Salmonella enteritis (1).

§ Pneumonia (25); pleural empyema (6).

‖ Pelvic abscess (16); peritonitis (8); prostatic abscess (4).

** Postoperative or posttraumatic thoracic (8); abdominal (7); lower extremity (3); vulva (1).

†† Cholangitis (10); acute cholecystitis (2).

‡‡ Necrotizing lesions in patients with profound neutropenia: tonsillitis (4); pharyngitis (4); cellulitis (3); enteritis (1).

§§ Meningitis (3); myonecrosis (1); pyoarthrosis (1); decubitus ulcer (1).

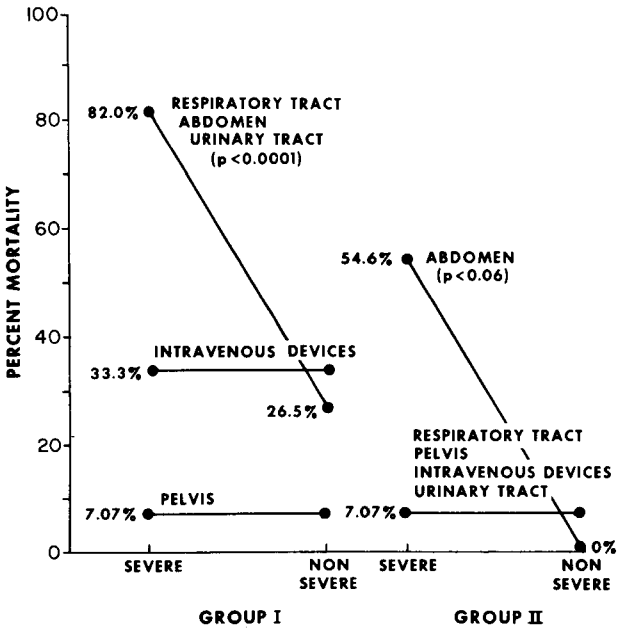

Fig. 2. Graph represents the relationship of incidence of mortality of infection to groups of underlying diseases, grade of illness attributed to infection, and the five most common portals of entry of bacteremia. For purposes of presentation in this graph, data of moderate and mild illness attributed to infection have been combined into a single category designated as nonsevere illness.

or grade of illness due to infection. In contrast, mortality was significantly higher for infections of the respiratory tract, urinary tract and those caused by contaminated intravenous devices in patients with advanced or terminal stages of incurable underlying diseases (Group I) than in patients who had potentially treatable or nonfatal underlying diseases (Group II) (p at least < 0.05).

The grade of illness due to infection had a significant influence on mortality for infections of the respiratory tract, abdomen, and urinary tract in patients with advanced or terminal stages of incurable diseases (Group I). For Group I patients, mortality of respiratory, abdominal, and urinary tract infections rated as nonsevere was 26.5% and rose to 82% in the severe form of infection ($p < 0.0001$). In contrast, the mortality of infections occasioned by intravenous devices in Group I patients was not significantly different when the illness was rated as severe or nonsevere.

Table 5 shows the relationship of the outcome of infection to the various categories of antibacterial chemotherapy and no antibacterial chemotherapy. Of the 285 episodes of gram-negative bacteremia, in five episodes (1.8%) infection subsided without antibacterial chemotherapy; the patients either had contaminated intravenous devices that were removed promptly or self-limited infections of the urinary tract. *Figure 3* is a graphic representation of the clinical course of one of those patients. Of the 285 episodes, in 24 episodes (8.4%) blood cultures became sterile before appropriate antimicrobial chemotherapy was started;

Table 5. Correlation of outcome of infection and the categories of antimicrobial therapy or no antimicrobial treatment

	Grade of illness attributed to infection; outcome						
	Severe		Moderate		Mild		
	Recovery	Death	Recovery	Death	Recovery	Death	Total
Group I*, therapy, no. episodes†							
Inappropriate	0	3	2	1	0	0	6
Appropriate	14	37	33 (5)	18 (1)	7 (3)	2	111 (9)
None	0	0	1	0	0	0	1
Indeterminate	1	5	4	5	1	1	17
Group II‡, therapy, no. episodes†							
Inappropriate	0	4	8	1	3	0	16
Appropriate	38 (5)	8	47 (6)	2	15 (4)	0	110 (15)
None	0	0	2	0	2	0	4
Indeterminate	6	2	7	0	5	0	20

* Group I—advanced or terminal stages of incurable underlying diseases.
† Number in parentheses is the number of episodes in which appropriate therapy was begun after blood cultures were sterile.
‡ Group II—potentially treatable or nonfatal underlying diseases.

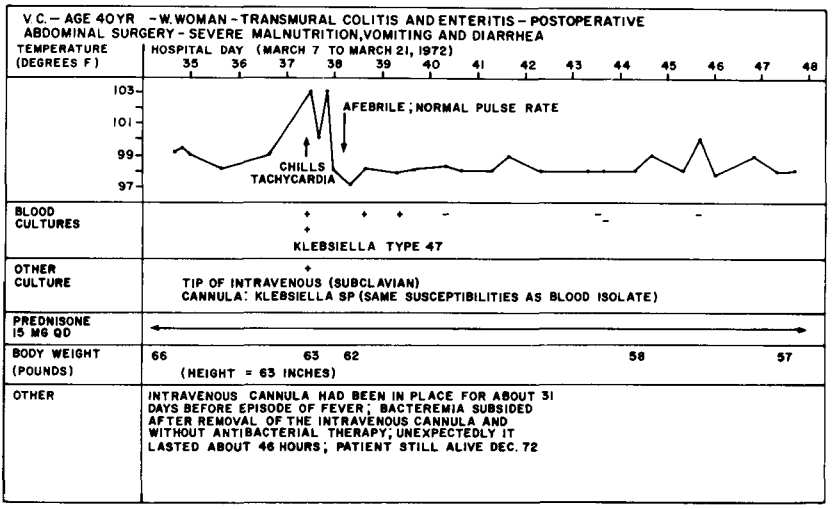

Fig. 3. Graph represents the clinical course of a patient with Klebsiella bacteremia caused by a contaminated intravenous cannula. After the cannula was removed, bacteremia subsided without antimicrobial therapy.

however, administration of appropriate antibacterial drugs usually was required for eradication of the underlying focus of infection.

Group II patients who received appropriate antibacterial chemotherapy had a significantly lower overall mortality (9.1%) than Group I patients

who received appropriate antibacterial chemotherapy (51.4%) ($p < 0.0001$). For each of the two categories of underlying diseases (Groups I and II) who received appropriate antibacterial chemotherapy, the percent fatality was highest for patients with severe illness due to infection, intermediate for those with moderate illness and lowest for those with mild illness (*Fig. 4*). However, the differences were statistically significant only when the groups with severe illness due to infection were compared to those with moderate and mild illness due to infection ($p < 0.0001$).

The grade of illness attributed to infection had a highly significant influence on the outcome of inappropriate antimicrobial chemotherapy. Of the 285 episodes of gram-negative bacteremia, inappropriate antimicrobial chemotherapy was administered in 22 episodes (*Table 5*). Of the 22 episodes, inappropriate antimicrobial chemotherapy was associated with the death of nine patients (40.9%) Of the seven patients in Groups I and II who had severe illness due to infection and inappropriate antibacterial chemotherapy, all died. Conversely, of the 15 patients in Groups I and II who had moderate or mild illness due to infection and who received inappropriate antibacterial chemotherapy, only two died. Thus, the mortality of patients in Groups I and II who had severe illness due to infection and inappropriate antibacterial chemotherapy (100%) was significantly greater than the mortality of patients in Groups I and II who had moderate or mild illness due to infection and who received inappropriate antibac-

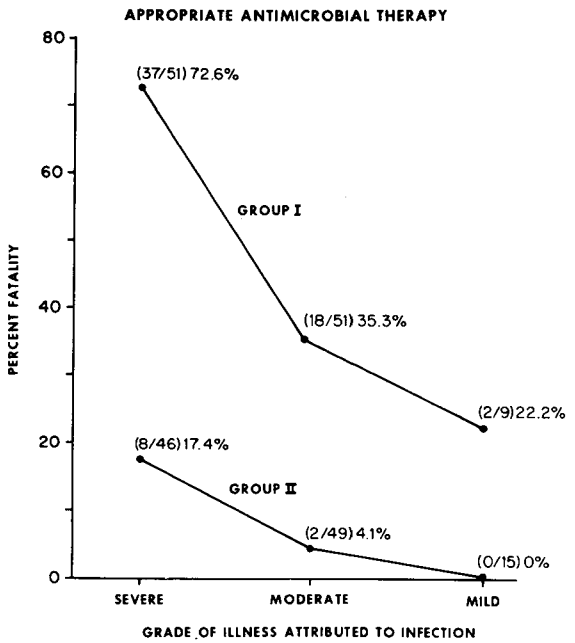

Fig. 4. Graph represents the percentage of fatality of infection related to episodes of gram-negative bacteremia treated with appropriate antimicrobial therapy by groups of underlying disease and grade of illness attributed to infection.

terial chemotherapy (13.3%) ($p < 0.0002$).

There was no significant difference in mortality among Group I patients who received appropriate or inappropriate antibacterial chemotherapy when the grade of illness due to infection was not taken into consideration ($p > 0.26$). However, in Group II, those patients who received appropriate antibacterial chemotherapy had a significantly lower overall mortality (9.1%) than those who received inappropriate antimicrobial chemotherapy (31.3%) ($p < 0.02$).

Discussion

There is considerable variability in the clinical course and outcome of bacteremia caused by gram-negative bacilli. The course of such bacteremia may be transient, intermittent, persistent, or recurrent. The process may be self-limited, curable by medical or surgical therapy or both, incurable because of inappropriate therapy, or fatal despite prompt appropriate therapy.

In most studies of large numbers of cases of gram-negative bacteremia, duration of bacteremia either has not been determined or has not been reported. The variable clinical course of bacteremia due to gram-negative bacilli may be delineated only by the practice of obtaining blood cultures repeatedly over the span of the patient's illness. For example, as a result of this practice, we found that in 10% of bacteremic episodes in our patients, blood cultures became sterile before appropriate antimicrobial chemotherapy was started or without any antibacterial chemotherapy. Conversely, in 16% of the episodes, bacteremia persisted for 7 or more days and usually continued, despite appropriate antibacterial chemotherapy.

Results of this study confirm the observation of McCabe and Jackson,[3] and others[4-9] that the grade of underlying disease of the patient is an extremely important determinant of outcome of gram-negative bacteremia. Furthermore, results of this study exemplified that patients classified on the basis of underlying disease could be subclassified into prognostically significant subgroups when the duration of bacteremia and the grade of illness attributed to infection were taken into consideration.

For each of the categories of underlying disease, mortality was lowest for patients with mild illness attributed to infection, intermediate for those with moderate illness, and highest for those with severe illness. The differerences were statistically significant when the groups with severe illness were compared to those with moderate or mild illness or both. Furthermore, a significantly higher mortality was associated with persistent bacteremia than with transient bacteremia in two large subgroups of patients: Group I patients (advanced or terminal stages of incurable underlying diseases) who had moderate illness caused by infection, and Group II patients (potentially treatable or nonfatal underlying diseases) who had severe illness due to infection. Contrary to expectation, there was no significant difference in mortality between transient and persistent bacteremia in Group I patients with severe illness. This could be attributed to the coexistence of two severe processes resulting in a highly fatal outcome.

Results of this study revealed that

infections of the pelvic cavity had the lowest overall mortality and fared similarly with appropriate management, regardless of the grade of underlying disease or the grade of illness due to infection. This could not be attributed to age or sex of the patients. In most of the patients, bacteremia was transient and lesions were readily accessible to pelvic drainage or evacuation. Of the three patients with pelvic infections who died, two had persistent bacteremia despite appropriate antibacterial chemotherapy. One of the two patients had a pelvic abscess and septic thrombophlebitis of the iliac vein and inferior vena cava at autopsy. The other patient died from necrotizing pneumonia which may have been caused by metastatic infection or by aspiration. The third patient had ovarian carcinomatosis, an incompletely drained pelvic abscess, transient bacteremia, and recurrent, bland pulmonary emboli. Other investigators also have noted the frequently transient nature and relatively low mortality of gram-negative bacteremia arising from infections of the pelvic cavity.[8, 14]

In contrast to pelvic infections, intraabdominal infections had a very high overall mortality. Furthermore, the grade of illness attributed to infection had a significant influence on the mortality from intraabdominal infections in both categories of underlying disease. Intraabdominal infections had no mortality in patients with potentially treatable or nonfatal underlying disease (Group II) and nonsevere illness due to infection. However, when the grade of illness due to infection in Group II patients was severe, the mortality for intraabdominal infection rose to 54.6%. For those patients with advanced or terminal stages of incurable underlying diseases (Group I), the mortality for intraabdominal infections rated as nonsevere was 33.3% and rose to 83.3% in the severe form of the infection. Difficulty in locating intraabdominal abscesses often caused delay in obtaining early adequate drainage. Other anatomic factors that appeared to contribute to mortality in some patients with intraabdominal infections were the presence of multiple abscesses; spread of infection to the liver, spleen, or extraabdominal sites; suppurative pylephlebitis; disruption of surgical anastomoses, enteric fistulas or wound dehiscence; and gastrointestinal hemorrhage. In some debilitated patients with abdominal carcinomatosis, generalized peritonitis or neoplastic abscesses were refractory to appropriate antimicrobial chemotherapy. In two patients in whom there was a functioning abdominal aortic prosthesis, the development of generalized peritonitis caused infection of the prosthesis. In one of the two patients, death was caused directly by dehiscence of the infected aortic prosthesis. In the other patient, evidence of infection of the aortic graft was found at autopsy.

In our patients with potentially treatable or nonfatal underlying diseases (Group II), infections of the urinary tract and contaminated intravenous devices appeared to be low-risk portals of entry for mortality regardless of the grade of illness caused by infection. Of 56 patients in Group II with bacteremia arising from the urinary tract or from a contaminated intravenous device, only two died. It has long been known that bacteremia

in association with urinary tract infection frequently is transient and self-limited.[21-23] Likewise, in our experience with patients in whom contaminated intravenous devices are present, bacteremia usually terminates promptly with extirpation of the offending agent, unless there is associated cellulitis, a suppurative endovascular lesion at the cannula site, or a metastatic lesion elsewhere in the body.

Infections of the urinary tract or those occasioned by contaminated intravenous devices did not convey the same low risk for patients with advanced or terminal stages of incurable diseases (Group I) as they did for patients with potentially treatable or nonfatal underlying diseases (Group II). Similar conclusions may be derived from analysis of the data of pulmonary infections. This only reemphasizes the critical role of impaired host defense mechanisms in determining outcome of gram-negative bacteremia from those portals.

Assessment of efficacy of antimicrobial therapy in patients with bacteremia caused by gram-negative bacilli may be exceedingly difficult. In some instances, unfavorable outcome may be attributed unjustifiably to the underlying disease rather than to the therapeutic regimen. In others, recovery may be attributed erroneously to antimicrobial chemotherapy in patients with self-limited infections. The latter is apt to occur in patients with nonsevere illnesses due to infection and transient bacteremias arising from the urinary tract or pelvis, from contaminated intravenous devices that are extirpated promptly, or from abscesses that are drained adequately without delay. Factors relevant to the lesion causing bacteremia should be considered in the evaluation of antimicrobial therapy. Also, it is important to grade the degree of illness caused by the infection as well as the extent of the underlying disease. Antimicrobial drugs are less likely to be effective in patients with severe illness caused by infection and incurable underlying disease than in those patients with gram-negative bacteremia who have nonsevere illness due to infection and potentially treatable or nonfatal underlying disease. Likewise, it is important to gauge the pre- and post-therapeutic behavior of the bacteremia itself by obtaining blood cultures immediately before and at repeated intervals after initiation of therapy. In some patients, blood cultures may become sterile even before therapy is started. In others, blood cultures may remain positive after initiation of therapy, even when signs and symptoms of clinical illness have diminished or subsided.[24] Persistently positive blood cultures, despite administration of antimicrobial drugs, suggest that the choice of drugs was incorrect (organisms are resistant), inadequate concentrations of the drug are being achieved at the site of infection, or that the source of bacteremia is not amenable to antimicrobial therapy alone.

The variable clinical course of bacteremia and the potential risks of antimicrobial therapy itself make it imperative that the clinician select which patients with suspected or proved gram-negative bacteremia should be treated with antimicrobials and which should not. It is our opinion that the majority should be treated; the aim being to eradicate bacteria

from the blood and from the distributing foci of infection. Two possible exceptions of the concept are: (1) occasionally it may be justifiable to withhold or discontinue antimicrobial therapy in patients clearly in the endstages of incurable diseases, when treatment of bacteremia may serve only to prolong agony and not to change the certainty of fatal outcome; and (2) in patients with mild illness and an obvious low-risk portal of entry of the pathogen, it occasionally may be justifiable to withhold potentially toxic antimicrobials pending the results of microbiologic studies. However, if the bacteremia persists or the clinical illness worsens while the patient is under frequent, careful observation, administration of antimicrobials becomes mandatory. When the clinical condition improves, bacteremia subsides promptly and the source of bacteremia is adequately treated by local measures, no systemic therapy may be required.

In our opinion, patients in whom prosthetic devices are present (e.g., hip prostheses, abdominal aortic grafts, prosthetic heart valves) represent a special therapeutic category. Antimicrobial chemotherapy should always be administered for treatment of gram-negative bacteremia even when the patient has mild illness due to infection, a low-risk portal of entry for bloodstream infection, and potentially treatable or nonfatal underlying disease. The possible devastating effects of metastatic infection of such prosthetic devices justify the potential risks of aggressive antimicrobial chemotherapy.

In conclusion, consideration of the variable clinical course of gram-negative bacteremia, knowledge of the prognostic factors, and an awareness of unique circumstances of patients may aid in decisions concerning management of patients with gram-negative bacteremia. Consideration of the variable clinical course and prognostic factors may also be of assistance in the analysis of the relative efficacy of various antibacterial drugs for treatment of the condition.

Summary

The course of 285 episodes of gram-negative bacteremia in 257 patients was studied clinically, microbiologically and, in many instances, at autopsy. Duration of gram-negative bacteremia was transient (<7 days) in 75.8% of episodes, persistent (7 to 46 days) in 16.1%, and indeterminate in 8.1%. In 10% of episodes, blood cultures became sterile either before appropriate antibacterial chemotherapy was started or without any chemotherapy. Underlying disease and grade of illness attributed to infection were major determinants of mortality. The overall fatality from infection was 31.2%. Persistent bacteremia significantly increased mortality for two large subgroups of patients. Pelvic portals had the lowest overall mortality and fared similarly with appropriate management, regardless of the grade of underlying disease or grade of illness due to infection. There was a significant correlation between the grade of illness attributed to infection and outcome of appropriate or inappropriate antibacterial chemotherapy. Knowledge of the variable clinical course and of these prognostic factors may aid in decisions concerning management of

patients with gram-negative bacteremia.

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