# "Aerobic" Gram-Negative Bacteremia: Control and Treatment

Medical Grand Rounds

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A. Gram Negative Bacteremia, DVAH, Jan-June, 1977

Case #1

J.L. is a 71 year old white male who presented to the Dallas VA Hospital in April 1977 with Placidyl overdosage, urinary tract infection, and obstructive uropathy. He had previously had a resection for carcinoma of the prostate one year earlier. When a second prostatic resection was performed on May 9, 1977, stones and purulent secretions were noted in the prostate. He did well postoperatively and was discharged on trimethoprim-sulfamethoxazole. However, his local physician again placed him on Placidyl. On May 29, he fell and hit his head. On arrival at the P-10 area at the VA Hospital, he was noted to have a temperature of 98°F and hypotension. His blood pressure responded to fluids. He had a urinary catheter inserted and 600 ml of urine was removed. An indwelling urinary catheter was inserted prior to his return to home. Within 10 hours, he developed a rigor and fever. On return to DVAH, his temperature was 103.4°F, blood pressure was 106/70; pulse rate was 120 and respirations were 24. The patient was oriented and alert. Examination of urine revealed pyuria with gram negative rods. The patient was begun on Penicillin and Gentamicin. Blood cultures were reported within 24 hours to be growing gram-negative rods. *Serratia marcescens* was identified later which was resistant to Gentamicin but sensitive to Amikacin. He was switched to Amikacin, but elevated temperature persisted for 5 days. An intravenous pyelogram showed that the kidneys moved well and the collecting systems were normal. No prostatic tenderness was noted. Repeat blood and urine cultures on the 4th day of Amikacin were negative. The patient eventually became afebrile and it was possible to remove his Foley catheter. He was discharged to be followed in GU Clinic with instructions not to take Placidyl.

This patient illustrates a number of features encountered with bacteremia due to gram negative bacilli:

(1) This patient developed bacteremia following drainage of an obstructed bladder rather than during the period of obstruction. A history of instrumentation has been commonly observed in patients with gram-negative bacteremia.

(2) His bacteremia was with a gentamicin-resistant organism, which may have been acquired on the Urology Service when hospitalized during May, although no urine culture was done post-operatively. A cluster of urinary tract infections with gentamicin-resistant organisms was investigated by the VA Infection Control Nurse on the urologic ward during April-May, 1977.

(3) Fever persisted longer than 3 days after treatment with an appropriate agent (Amikacin). Since it is unusual for fever to persist longer than 3 days following urinary tract infection (1) or bacteremia, he represented a problem in determining how to approach a person with fever after gram-negative bacteremia.

In this presentation, gram negative bacteremia (GNB) is bacteremia with gram-negative bacilli from the families of *Enterobacteriaceae* or *Pseudomonadaceae*. The *Enterobacteriaceae* are facultatively aerobic organisms which can grow anaerobically; hence a positive blood culture for a gram-negative bacillus in an anaerobic bottle does not necessarily mean a strict anaerobic, as *Bacteroides fragilis*, but can be *E. coli*, Klebsiella, etc. These organisms generally grow out in 1-2 days. Pseudomonas species are oxidase-positive gram-negative organisms which will grow only in an aerobic blood culture bottle. They may require 3 days or more to grow.

TABLE 1

Gram-Negative Bacteremia (GNB) - Dallas VA Hospital

Jan - June 1977

| | Medical (%) | Surgical (%) | Total (%) |
|---|---|---|---|
| | % | % | % |
| Total Admissions | 5263 | 2630 | 7893 |
| Cases with GNB | 49 (.9) | 21 (.8) | 70 (.9) |
| Community acquired | 25 | 5 | 30 |
| Hospital associated | 24 | 16 | 40 |
| Total Deaths | 264 | 77 | 341 |
| Case fatality - GNB (ratio) | 16 | 8 | 24 (34)* |
| Case fatality - GNB Community | 6 | 1 | 7 (23) |
| Case fatality - GNB Hospital | 10 | 7 | 17 (43) |

* Case fatality per 100 cases of GNB

TABLE 2

Frequency of Gram-Negative Bacteremia, DVAH*

| | Medical No. (%) | Surgical No.(%) | Total No. (%) | Case fatality ratio (per 100) |
|---|---|---|---|---|
| *Escherichia coli* | 21 (39) | 6 (21) | 27 (33) | 30 |
| Klebsiella-Enterobacter | 14 (26) | 8 (27) | 22 (27) | 44 |
| Pseudomonas | 6 (11) | 8 (28) | 14 (17) | 36 |
| Proteus | 10 (19) | 3 (10) | 13 (16) | 38 |
| Serratia | 3 (5) | 4 (14) | 7 (8) | 43 |
| Polymicrobial | 5 | 6 | 11 | 64 |
| Total | 54 (100) | 29 (100) | 83 (100) | |

* 70 patients, 11 with polymicrobial GNB, of whom two had three organisms, or total of 83 with GNB.

The frequency of gram-negative bacteremia per total admissions (0.9%) during Jan-June, 1977 at the Dallas VA Hospital was comparable to that in previously reported series (2). The Surgical Service had a higher proportion of cases which were hospital-associated, but the frequency of these per admission was nearly equal on surgery (0.6%) as that on the Medical Service (0.5%). Cases from nursing home were considered community-acquired, although in many respects they resemble hospiral-associated cases, i.e., resistant organisms, case fatality. *Escherichia coli* was the major causative organism on the Medical Service, particularly in community-acquired patients, whereas Pseudomonas and Klebsiella predominated in hospital-associated surgical cases. The case fatality ratio was not influenced by the particular causative organism, but was greater in hospital-associated cases and in those with polymicrobial bacteremia. Persistent gram-negative bacteremia for longer than 3 days after appropriate therapy was noted in five patients (7%) in the group.

TABLE 3

Antimicrobial Susceptibility of Gram-Negative Bacilli

DVAH, January - June 1977

| | | # of Strains Susceptible | | | |
|---|---|---|---|---|---|
| | | | | Hospital | |
| Antimicrobial Agent | | Total Group | Community | Medical | Surgical |
| Gentamicin | | 77 | 89 | 77 | 57 |
| Kanamycin | | 66 | 81 | 69 | 38 |
| Streptomycin | | 65 | 72 | 73 | 30 |
| Chloramphenicol | | 63 | 75 | 62 | 30 |
| Doxycycline | | 63 | 64 | 73 | 48 |
| Carbenicillin | | 54 | 75 | 43 | 33 |
| Tetracycline | | 54 | 58 | 65 | 33 |
| Cephalothin | | 45 | 58 | 50 | 14 |
| Ampicillin | | 19 | 25 | 23 | 5 |
| | Number Tested | | | | |
| Amikacin | 18 | 89 | 60 | 100 | 100 |
| Tobramycin | 18 | 11 | 0 | 0 | 12 |

Gentamicin remains the most appropriate antimicrobial agent for those organisms causing bacteremia acquired in the community. However, it was the appropriate agent during this period of time for slightly more than one-half of the hospital-associated cases on the Surgical Service. Amikacin, a recently introduced aminoglycoside was effective against the gentamicin-resistant organisms whereas tobramycin was not very effective. (These aminoglycosides were only tested against gentamicin-resistant strains.) Other aminoglycosides were slightly less active *in vitro* as were other broad spectrum agents, such as the tetracyclines. Two agents, cephalothin and ampicillin, would have been poor choices for empiric treatment of suspected bacteremia cases.

B. Clinical Manifestations of Gram-Negative Bacteremia (Table 4)

TABLE 4

Clinical Features Suggestive of Gram-Negative Bacteremia

Patient with fever and chills with either
hypotension, oliguria or tachypnea
Fever following instrumentation
Thrombocytopenia without apparent cause
Acidosis without apparent cause
Change in mentation without apparent cause

Gram-negative bacteremia should be suspected when any patient with fever and chills develops either hypotension, oliguria or tachypnea (3). Unfortunately, these features are not pathognomonic of septicemia due to GNB. Up to one-third of cases with bacteremic shock are caused by gram-positive organisms (4), anaerobic bacteria (5) and even candida (6). Patients with gram-negative bacteremia will frequently have volume depletion so it may be difficult to distinguish hypotension on basis of bacteremia from that due to volume depletion. Oliguria may be seen even in the absence of hypotension (7), probably as the result of shunting of blood flow within the kidney. Tachypnea is a predictable hallmark of sepsis due to gram-negative bacteria; frequently these patients are initially considered to have pneumonia. Fever immediately following urinary instrumentation (as in Case #1) should be considered to be gram-negative bacteremia. The development of thrombocytopenia, acidosis, or central nervous system changes without any apparent cause may be a clue to sepsis. These findings are illustrated by the following case:

Case #2

T.D. was a 47 year-old retired Marine Sergeant who was admitted to the Dallas VA Hospital in February, 1976 with a history of congestive heart failure. The patient had spent approximately ten years in Asia including two tours in Viet Nam prior to discharge seven years earlier. He was treated initially with digitalis and diuretics. Four days after admission, his temperature rose to 102°F. Initial blood cultures were negative and the patient became afebrile. However, on the tenth hospital day, the patient became febrile again and on the following day he developed hypotension, oliguria, and mental confusion. He was noted to have muscle tenderness with a striking elevation of SGOT, consistent with rhabdomyolysis. Blood cultures were positive for pseudomonas species, which was later identified by the Texas State Health Department as *Pseudomonas pseudomallei*. This organism was resistant to all antibiotics tested save doxycycline. He underwent hemodialysis for treatment of acute renal failure. His blood pressure had to be maintained with dopamine with subsequent ischemic changes on the tip of his toes. Antibiotics were stopped following treatment of his initial bacteremia. However, on the 30th day he again developed fever and thrombocytopenia. Blood cultures again demonstrated the pseudomonas species. At this time he was placed on a combination of doxycycline, carbenicillin and gentamicin. His course was complicated by supraventricular tachycardia

which required cardioversion. His renal function improved so that dialysis could be discontinued. He eventually became afebrile and repeat blood cultures on therapy were negative. After discharge he presented again with fever, chills and bone tenderness in May, 1976. Blood cultures were positive again. At this time the state laboratory confirmed that this patient had melioidosis which he likely contacted on a tour of duty in South Viet Nam more than seven years earlier. Long-term therapy with tetracycline and trimethoprim-sulfamethoxazole was instituted. His initial febrile illness was proven serologically to be influenza A infection. Microbial synergism of these two infections has been discussed previously by Dr. Mackowiak (8).

This patient presented with virtually all of the possible complications of gram-negative septicemia, although the causative organism was a highly unusual one which was contacted outside the United States. On one occasion the hematologists made the accurate clinical diagnosis of gram-negative bacteremia when thrombocytopenia occurred with fever approximately twenty days after the original onset of bacteremia. At this time, the patient had high levels of serum antibody to the lipopolysaccharide of the infecting organism.

TABLE 5

Clinical and Laboratory Characteristics of Septicemia due to Gram-Negative Bacteremia

| | |
|---|---|
| Cardiac: | Myocardial - Chest pain, ST-T wave abnormalities<br>Hemodynamic - Early: normal to high cardiac output;<br>Late: decreased cardiac output with cyanosis |
| Metabolic: | Early - alkalosis (respiratory), hyperglycemia, hyperlipedemia<br>Late - acidosis with increased blood lactate |
| Pulmonary: | Hyperventilation, respiratory alkalosis, hypoxia, acute respiratory distress syndrome (shock lung) |
| Renal: | Oliguria with or without hypotension, renal failure, reduced clearance amylase |
| Hepatic: | Elevated SGOT, rarely elevated bilirubin |
| Gastro-intestinal: | Diarrhea |
| Central Nervous System: | Confusion, mental obtundation |
| Hematologic: | Leukocytosis with toxic granulation, vacuolation, Döhle bodies, rarely leukopenia; thrombocytopenia; with shock: reduced C3, C5, C6, C9, Factor B,and properdin. |

The most significant hemodynamic effect of gram-negative bacteremia is the development of shock (3, 7). Although patients with gram-positive bacteremia can present with shock, a significantly higher pulse rate and a higher cardiac index occurs in these patients than in those with gram-negative bacteremia (4). Very low cardiac indices are seen exclusively in patients with gram-negative bacteremia. In the early course of bacteremia shock, although a normal-to-high cardiac output may be present, it is inadequate (4, 9). This condition likely results from peripheral pooling and decreased venous return although different studies have found either normal or decreased vascular resistance (4, 9). The late stage of bacteremic shock is characterized by a lowered cardiac output with cold extremities, cyanosis and acidosis with elevated blood lactic acid levels (9). There is no satisfactory explanation for the observation that some present initially with this late stage of shock (4). Hypoxia and hyperventilation with respiratory alkalosis are present in the majority of patients. Less commonly patients progress to have the acute respiratory distress syndrome, in the past referred to as shock lung (3).

The clinical and laboratory abnormalities that are seen likely result either from decreased vascular perfusion secondary to peripheral pooling or to substantial shunting of blood in the capillary exchange beds (9). The latter likely accounts for the cardiac, renal, gastrointestinal and central nervous system abnormalities that are characteristic of bacteremic shock. Oliguria may be seen in the absence of hypotension (7). An elevated creatinine and impaired creatinine clearances may develop subsequently. An illustration of the time course of renal function abnormalities following acute experimental injury is seen in Figure 1 (Robert Cronin, to be published). Hence, creatinine values may change dramatically if oliguria was present and should not be considered drug toxicity alone. In addition, reduced clearance of amylase

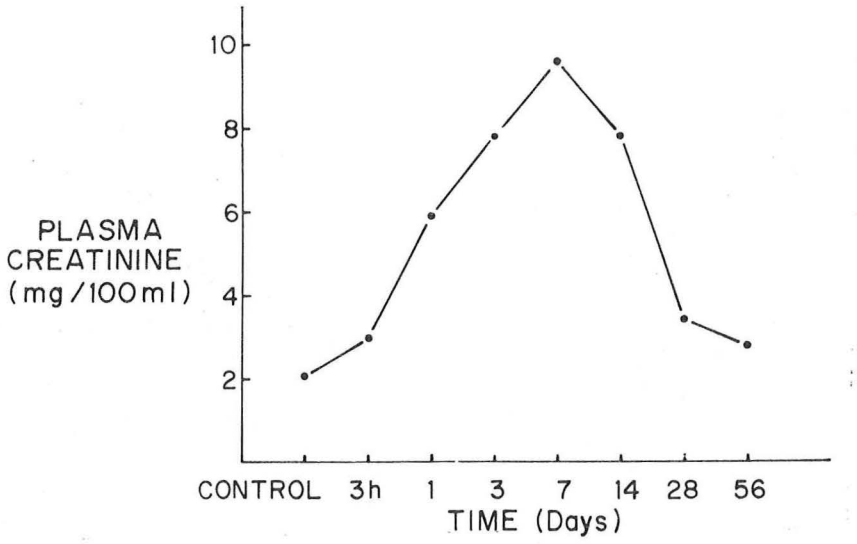


FIGURE 1

may occur so that an elevated serum amylase may not necessarily indicate pancreatitis. The presence of diarrhea or even bloody stools may follow bacteremia shock without evidence of primary gastrointestinal disease. Metabolic effects include hyperglycemia and hyperlipedemia. The lowered insulin-glucagon ratio in patients with bacterial infections indicates that the beta cells are unable to compensate fully for the hyperglucagonemia (10). The hyperlipedemia primarily represents increases in triglycerides as well as cholesterol and is seen exclusively in gram-negative infections (11).

Hematologic manifestations have been extensively reviewed (3). The early response to gram-negative bacteria is leukopenia. Sequestration of neutrophils primarily in the pulmonary circulation is responsible for this effect of LPS, and presumably of bacteria (12), and is probably mediated by complement (13). However, most patients present with leukocytosis. Toxic granulation has been noted in a majority, and slightly less than one-half have Dohle bodies (blue inclusions in cytoplasm of neutrophils) and vacuolization (14). None of these tests are specific for gram-negative infections although vacuolization has been stated to be relatively specific for bacterial infections. Polymorphonuclear leukocyte chemotaxis is impaired in patients with bacterial (including gram-negative) infections (15). Impaired opsonization, due to plasma factors, has been detected in a small number of patients (16). Thrombocytopenia occurs in up to 50% of patients with gram-negative bacteremia, but striking depressions are seen only in those patients with shock and the syndrome of disseminated intravascular coagulopathy, seen in 5-10% of patients with gram-negative bacteremia (3). Diminished complement levels (less than 100 mg/dl) were observed in those with shock and in those who had a greater likelihood of dying (17). The diminished complement level represents activation of the alternate complement pathway (properdin pathway) since levels of properdin, factor B and C5 and C6 and C9 are also significantly decreased in patients with shock (18). There are pronounced changes in the kallikrein system with decrease in both kallikrenogen and kallikrein inhibitor (19). Bacterial products likely act through Hageman factor to activate the kallikrein system and the interrelated systems of coagulation, complement, and fibrinolysis (3). This interaction accounts for the unique hemodynamic effects following bacteremia with gram-negative bacilli.

These effects in gram-negative bacteremia have been presumed to relate to the effect of lipopolysaccharide, or endotoxin (20),a component of the cell wall (Figure 2, page 8). Several lines of evidence have indicated that this compound is a significant mediator of the clinical syndrome of bacteremic shock with aerobic gram-negative bacilli.

(1) There is a remarkable similarity in the clinical manifestations following gram-negative bacteremia and experimental changes which occur following administration of lipopolysaccharide (12). Expermental studies have shown that the toxic moiety of the lipopolysaccharide is the lipid A portion (Table 6) (21).

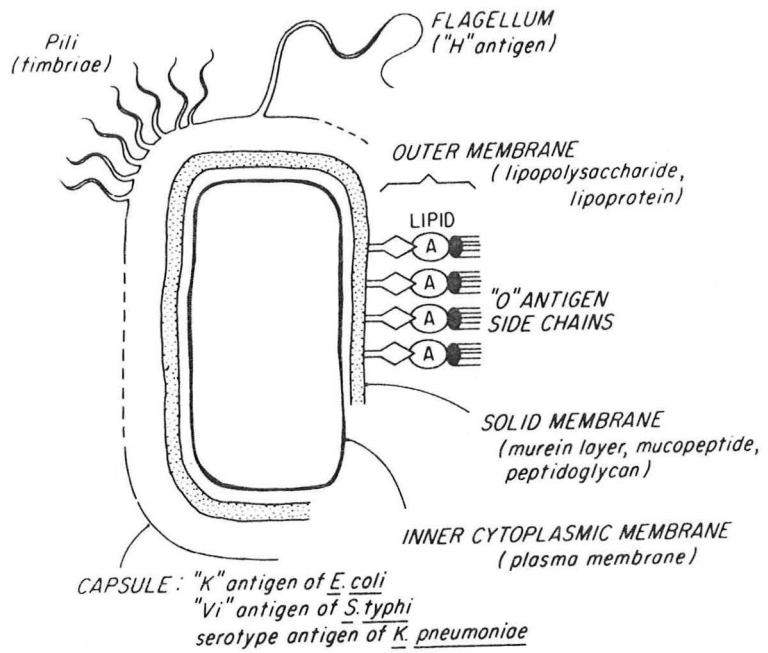


FIGURE 2: Major cell wall antigens of the Gram-negative bacillus

TABLE 6

Biological Effects of the Lipid Moiety of
Lipopolysaccharide (Endotoxin)

| | |
|---|---|
| Pyrogenic | B Lymphocyte stimulation |
| Lethality | Macrophage activation |
| Hypotension | Interferon release |
| Schwartzman phenomenon | Complement activation |
| Leukopenia and leukocytosis | Induction of Prostaglandin synthesis |
| Thrombocytopenia | Limulus lysate gelation |

(2) Protection in experimental animals against the complications of gram-negative bacteremia can be elicited following passive and active immunization with the purified lipopolysaccharide (22). Curiously, antibody to lipid A does not account for this protection but rather antibody to the KDO portion of the core polysaccharide (Figure 3).

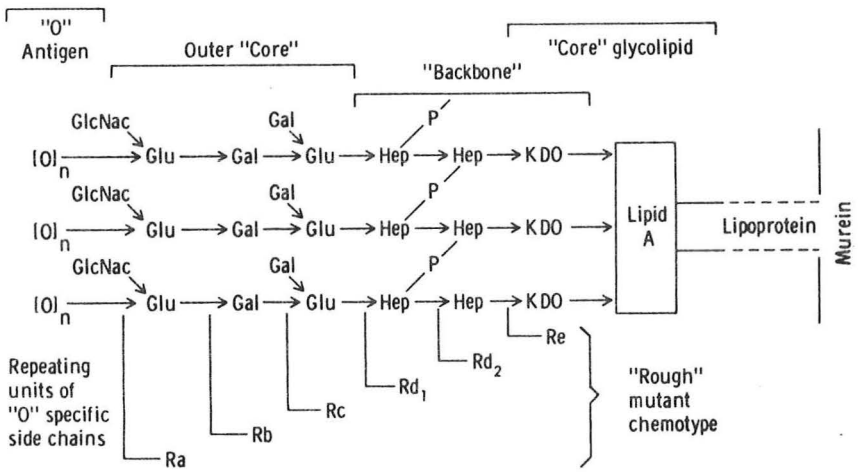


FIGURE 3

(3) The hematologic manifestations in patients with shock bear a remarkable resemblance to experimental effects following lethal doses of the lipopolysaccharide (12, 17, 23).

Hence, a major effort has been expended to develop an assay for endotoxin in patients of the gram-negative bacteremia. Thus far, no one has been able to detect the extremely small quantities of endotoxin that presumably circulate during the course of infection with either radio-immunoassay, mass spectography or gas chromatography. However, an indirect test, the limulus lysate gelation test, has been a sensitive indicator of endotoxin activity in experimental situations (24). Initial clinical reports of the use of the assay showed a correlation with gram-negative bacteremia; however, further studies indicated that the test was not specific for gram-negative bacteremia. False positive reactions were noted in individuals with gram-positive infections and even in some patients without fever or bacteremia (25). One extremely well-controlled study determined that a positive

test correlated better with leukocytosis and liver function abnormalities (26) whereas another showed a significant correlation between a positive test and presence of leukopenia or thrombocytopenia and mortality (5). Furthermore, a positive test requires nearly as long as a positive blood culture and there is poor standardization of the test. Hence it has had limited clinical usefulness. It has been found to be useful for routine screening of pharmaceuticals and other parenteral solutions (12).

Other low molecular weight substances are produced by *Enterobactericeae* which are chemotatically active for neutrophils and mononuclear cells (reviewed in 27). These activity biological materials are similar to lymphokines produced by stimulated lymphocytes and may be active biological compounds along with the more highly characterized moiety: lipopolysaccharide. The gram-negative bacillus is an exceedingly complex structure which can release a number of components from the outer membrane which play a role in the clinical symptom-complex of bacteremic shock. Lipopolysaccharide may not be the exclusive mediator, but rather the best characterized experimentally.

C. Factors Affecting Prognosis with Gram-Negative Bacteremia (Table 7)

TABLE 7

Factors Adversely Affecting Prognosis with Gram-Negative Bacteremia

Hospital-associated bacteremia
Presence of rapidly fatal disease
Presence of heart disease
Shock at onset of sepsis
Shock with enteric source of infection
Shock with pulmonary failure or low cardiac output
Polymicrobial sepsis
Inappropriate antibiotic
Use of bacteriostatic antibiotic in patient with rapidly fatal disease

Bacteremia in the hospital bears a worse prognosis than community acquired, doubtless because bacteremia occurs in patients with other complications and failure to thrive for many reasons. Individuals with rapidly fatal disease such as acute leukemia have significantly higher case fatality ratio (Table 8, p.11), than do those with no underlying disease. The principal determinant in these immuno-suppressed patients is neutropenia (5). Another underlying disease which significantly affects the outcome is the presence of heart disease, as manifested by either cardiomegaly, left ventricular hypertrophy or atrial fibrillation (9). The cardiac output at time of presentation appears to be a major determinant of survival when patients have shock (9). Diminished cardiac output with shock may

TABLE 8

Case Fatality Rates in Bacteremia by
Causative Organism and Underlying Disease (28)

| | % | | |
|---|---|---|---|
| | Non Fatal | Ultimately Fatal | Rapidly Fatal |
| *E. coli* | 6 | 38 | 70 |
| Kleb-Enterobacter | 11 | 36 | 83 |
| Proteus | 5 | 50 | - |
| Pseudomonas | 22 | 67 | 92 |
| Polymicrobial | 57 | 61 | 33 |

account for increased case fatality ratio in the elderly (7). Those individuals who present with shock have a poor prognosis, especially if the source of the infection is the gastrointestinal tract or if they develop respiratory distress syndrome (shock lung) (9).

The outcome does not relate to the causative organism but rather to the severity of the underlying disease (Table 8). Bacteremia with pseudomonas species does not bear the ominous prognosis in patients with non-fatal diseases, whereas it is invariably fatal in the neutropenic patient. An ominous sign in these latter patients is the development of ecthyma gangrenosum, secondary to invasion of the blood vessels by Pseudomonas. Bacteremia with more than one gram-negative organism (polymicrobial) is equivalent to having an ultimately fatal disease since the case fatality rate for polymicrobial bacteremia patients with nonfatal diseases (57%) was similar to patients with ultimately fatal infections (Table 8). Dr. Mackowiak has recently reviewed cases of polymicrobial bacteremia at DVAH. The patients were generally elderly and in all cases had a significant underlying disease, although not all were considered to have an ultimately fatal one. Case fatality rates were higher in patients with ultimately fatal infections, such as malignancy, patients who had either pulmonary or enteric source of infection, and in those who had hospital-associated infections. The combination of two or more gram-negative bacilli or of a gram-negative organism with a fungus carried a worse prognosis than the combination of a gram-negative bacillus with Enterococcus, which occurred frequently.

Appropriate antibiotics do improve prognosis, particularly if antibiotics are used prior to the development of shock (7, 25). Appropriate antibiotics may not make a difference after the appearance of shock (7). Antimicrobial susceptibility tests correlate reasonably well with clinical response in patients without a rapidly fatal disease; the only exception is with *Salmonella typhosa*. Chloramphenicol or ampicillin are effective in therapy of typhoid fever, but other antibiotics are not clinically useful even though effective *in vitro*. Appropriate bactericidal antibiotic has been more effective than bacteriostatic antibiotics in neutropenic patients with underlying disease (5, 25).

D. Approach to Patient with Presumed Bacteremic Shock.

1. Establish Presumptive Diagnosis - etiologic considerations:

(a) Hypovalemia due to hemorrhage, dehydration, or loss of protein
(b) Myocardial failure due to myocardial infarction, cardiac arrhythmia
(c) Anaphylaxis due to hypersensitivity
(d) Neurogenic shock
(e) Impediment to blood flow, either due to pulmonary embolization or dissecting aneurysm
(f) Adrenal insufficiency

Remember: bacteremic or septic shock may be a primary consideration but it also is a diagnosis of exclusion initially, pending results of blood culture.

2. Obtain at least two blood cultures from separate vein puncture site and other appropriate cultures. If the patient is disorientated, a lumbar puncture must be done to rule out meningitis. Gram-negative bacteremia is an extremely uncommon cause of meningitis save in the neonate. Consideration should be given to paracentesis to rule out peritonitis. Other workup would include: three way x-ray of the abdomen, sonography and liver-spleen scan.

3. Insert indwelling urinary catheter, attach to sterile closed drainage system, and record urine flow at hourly intervals. The goal is to maintain urine flow of 50 ml/hour.

4. Fluid Volume Replacement - Start 1000 ml of Ringer's lactate or saline; infuse in 15 minutes unless congestive failure present (29). Consider use of whole blood if loss of blood has occurred. Plasma volume expansion has been shown to produce significant effects on mean arterial blood pressure, central venous pressure, cardiac index, stroke volume and to decrease systemic vascular resistance (4). In this study, up to 40% of patients with bacteremia and shock recovered following volume expansion. During volume expansion, pressor agents should not be added or if they are being given, the rate of administration should not be changed. If pressor agents are added during this period, then the effect of volume expansion can't be determined.

5. Insert central venous pressure catheter or a flow directed pulmonary artery catheter (Swan-Ganz) for pulmonary artery and capillary wedge pressure (29). The central venous pressure catheter gives at best an indirect measurement of pulmonary wedge pressure and may give misleading measurements. Pulmonary wedge pressures are much more reliable for predicting left ventricular competence but inserting the Swan-Ganz catheter requires expertise and time. Administer fluid until increase of CVP to greater than 15 cm $H_2O$ or levels of > 22 mm Hg wedge pressure, which suggests critical levels of LV competence. Fluids should be continued at a rate of 15-20 ml/min until shock abates or CVP increases to > 15 cm $H_2O$.

6. Ventilation - supplemental oxygen with or without assisted ventilation, endotracheal intubation. Observe carefully for development of acute respiratory distress syndrome (shock lung).

7. If volume expansion fails or if CVP rises above 15 cm $H_2O$, utilize vasoactive agents.

(a) Dopamine, a precursor of norepinephrine is presently the treatment of choice (4, 9). This agent is a moderately active vasoconstricting agent for skeletal and skin blood vessels but acts to vasodilate renal and mesenteric vessels, resulting in increased renal and mesenteric blood flow (4). It is an active inotropic agent which increases myocardial contractility and cardiac output (4). Urine flow may be maintained even in the absence of elevation of arterial pressure. In fact, one should maintain the arterial pressure approximately 20-30 mm Hg less than normal for that patient in order to avoid excessive arterial vasoconstriction (9). Dopamine is administered in amounts ranging from 2 to 10 micrograms per kilogram per minute. Higher doses than this may inadvertently induce vasoconstrictive action due to its adrenergic effect. If chest pain develops, the dose should be diminished. A complication that may develop is necrosis of the tips of fingers or toes secondary to peripheral vasoconstriction, seen in patient #2.

(b) Isoproterenol has been an important second line agent because of its inotropic action. However it has the potential risk of inducing tachycardia and cardiac arrhythmias. In clinical situations, it has not been as successful in eliciting the appropriate clinical response although it would be of particular value in those individuals with expanded plasma volume (4). Its use would be contraindicated in individuals with volume depletion. Neither levarterenol (Levophed) nor metaraminol bitartrate (Aramine) are indicated presently for treatment of bacteremia shock (4, 9). These agents tend to cause peripheral vasoconstriction, lead to local tissue necrosis and compromise renal blood flow.

(c) The use of corticosteroids in the management of bacteremic shock remains controversial and I find little evidence to justify their use. Critical evaluations of favorable studies do not lend credence to their efficacy in bacteremic shock. In some studies which find evidence for efficacy, patients were not stratified by those factors which adversely affect prognosis (9) (Table 7). One recent study did analyze data by treatment groups and found significant improvement in each category. However, patients were not treated with other recommended modalities of therapy (fluid and vasoactive agents) initially. Furthermore, the authors did not consider the prospective study to be convincing enough, so an uncontrolled prospective study was included to shore up the data (30). Justification for the use of steroids has been that steroids increase cardiac output and suppress the systemic reaction to lipopolysaccharides (9). However, critically acceptable studies do not demonstrate beneficial effect of steroids on hemodynamic measurements (4). Cardiac output and renal perfusion are more effectively treated with dopamine. The appropriate experimental evaluation of efficacy of corticosteroids would require administration of steroids/placebo after volume expansion, and addition of dopamine, with groups stratified by risk categories.

If one is persuaded by the studies that their use is justified, or wishes to administer them as a last ditch effort, then one should administer large doses, as 40 mg dexamethasone or 200 mg methyl-prednisolone intravenously initially followed by 20 mg dexamethasone or 100 mg methyl-prednisolone intravenously every four to six hours for 24 hours. Use for this short period does not result in adverse side effects.

8. Appropriate antibiotic for gram negative bacteremia. The usefulness of appropriate antibiotics has been demonstrated (7, 25). Appropriate antibiotics enhance survival rates for those who have non-fatal and ultimately fatal infections. Appropriate therapy for those with rapidly fatal disease, such as the neutropenic leukemic patient, with an antibiotic with bactericidal activity enhances survival. The combination of carbenicillin and an aminoglycoside (gentamicin or amikacin) has been shown to be more effective than single-drugs for patients infected with pseudomonas, neutropenic patients and those with rapidly fatal disease (5, 31). In addition, the combination of a cephalosporin and an aminoglycoside was more effective for Klebsiella infections. Unfortunately, Table 9 shows that only a small proportion of organisms from bacteremic cases at DVAH were susceptible to both aminoglycoside and either carbenicillin for Pseudomonas or cephalosporin for Klebsiella.

TABLE 9

Antimicrobial Susceptibility of
Gram-Negative Bacilli

DVAH, Jan - June, 1977

| | *E. coli* | Klebsiella | Entero-bacter | Proteus | Pseudo-monas | Serratia |
|---|---|---|---|---|---|---|
| Gentamicin | 96 | 67 | 50 | 77 | 71 | 57 |
| Kanamycin | 96 | 67 | 50 | 85 | 0 | 57 |
| Streptomycin | 81 | 78 | 75 | 85 | 0 | 43 |
| Chloramphenicol | 89 | 67 | 75 | 77 | 7 | 29 |
| Doxycycline | 89 | 83 | 75 | 15 | 21 | 71 |
| Carbenicillin | 85 | 0 | 25 | 85 | 36 | 57 |
| Tetracycline | 89 | 78 | 75 | 15 | 0 | 29 |
| Cephalosporin | 74 | 56 | 0 | 54 | 0 | 0 |
| Ampicillin | 41 | 0 | 0 | 31 | 0 | 14 |
| Amikacin | 100 | 100 | 100 | 100 | 100 | 50 |
| Tobramycin | 0 | 0 | 0 | 0 | 50 | 0 |

In spite of this discouraging *in vitro* information, we would continue to recommend the combination of an aminoglycoside plus carbenicillin in a neutropenic patient with fever. If this person presented with a pulmonary infection, cephalosporin should be added to this combination since klebsiella is a commonly encountered cause of bacterial pneumonia in such cases and carbenicillin is ineffective against this organism. DVAH physicians are made aware of susceptibility of blood isolates as soon as bacterial species is known,and

for other cultures than blood, susceptibility results actually precede identification. Hence it is not necessary to know all the details of this table. Colistin is not listed since it is too toxic and should not be used at the present time. The major present problem is to recognize when a gentamicin-resistant organism is possibly responsible for the infection. We would continue to recommend gentamicin unless the patient with fever has previous isolates with proven gentamicin-resistant organisms or if the patient develops the febrile illness after prolonged residence in an area known to have gentamicin-resistant strains (i.e., SICU when other patients have these strains). Such activity at the Dallas VA Hospital has been noted in the surgical intensive care units on two separate occasions: in the fall of 1975 and the spring of 1977. Patients with significant infections including bacteremia occurred primarily in patients residing in SICU for periods exceeding 7 days.

(a) Gentamicin Blood Levels: Who should be monitored? Gentamicin blood levels are presently available in most of the Dallas area hospitals. The DVAH and PMH laboratories use microbiologic assays, although some recommend the radioimmunoassay (31). Monitoring of blood levels has been recommended because of the low therapeutic-toxicity ratio of this important aminoglycoside, especially with the frequency with which patients develop renal function abnormality. Nephrotoxicity has been found in up to 8% of those receiving gentamicin although many of these have been hypotensive or have received other nephrotoxic drugs (31). Retrospective studies indicate that the development of ototoxicity correlates with renal function abnormality (32). Two studies have critically evaluated gentamicin blood levels and the development of renal function abnormality. Dahlgren and associates noted that 36% of patients with valley (trough) levels exceeding two μg/ml developed a rise in creatinine; conversely, no patient with a valley level under 2 μg/ml developed rising creatinine (33). Renal toxicity did not correlate with peak levels. Peak levels related to the initial (loading) dose of gentamicin (Figure 4, page 16). A loading dose of greater than 1.2 mg/Kg was required to achieve 4 μg/ml, and 2.0 mg/Kg led to levels of 5 μg/ml, a more appropriate level. (In tests at the DVAH by Dr. Cohen, most of our peak values have been less than 4 μg/ml, indicating inadequate loading dose.) Rises in both peak and valley blood levels occurred in patients over a 7 to 10 day course of therapy although the rise was not considered important unless patients were treated for longer than 14 days (33). It was noted that one-third of their patients who received a maintenance dose of 1.5 mg/Kg q. 8 hours (after a loading dose of two milligrams per kilogram) developed an elevated creatinine within the first week of treatment. Hence, they recommended that a safer maintenance dose might be 1.3 mg/Kg every eight hours, especially after 72 - 96 hours of therapy. Goodman and associates noted that 44% of patients with impaired renal function developed nephrotoxicity (34). They evaluated the administration of gentamicin at PMH by two different methods, a variable frequency regimen (interval increased with elevated creatinine)

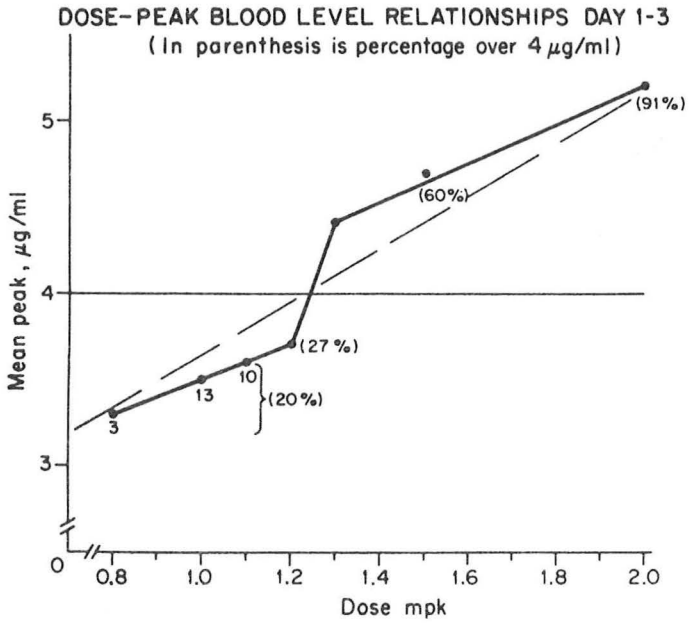


FIGURE 4: Mean peak levels and dose level. The values in parenthesis indicate the percentages over 4 μg/ml (33).

and a variable dosage regimen (reduced maintenance doses given to patients with impaired renal function). No difference was noted in the risk of renal toxicity with either of the two regimens; however, 50% of patients with a trough level greater than 2 μg/ml, and 70% of those with a trough level of greater than 4 μg/ml developed renal toxicity. A variability in peak serum levels was observed and did not correlate with renal toxicity. Thus, both studies indicate that elevated trough levels detect those patients who are at risk of developing increased renal toxicity. However, the majority of patients with nephrotoxicity due to gentamicin and amikacin developed elevated serum creatinine levels before antibiotic blood levels were available. Furthermore, the serum creatinine is "readily available, reproducible and inexpensive." (35).

Amikacin nephrotoxicity was noted in one third of patients with elevated trough levels (exceeding 10 μg/ml) and as with gentamicin, lower levels were rarely associated with nephrotoxicity (31). Ototoxicity as determined by pre and post-treatment audiograms occurred in 20% with amikacin and 13% with gentamicin, although only one patient of 34 had clinical hearing loss. Changes in audiograms did not correlate with elevated amikacin (>10 μg/ml) or gentamicin (>2 μg/ml) "trough" levels. Development of ototoxicity with amikacin had a positive correlation with total dose of therapy and a history of previous exposure to an aminoglycoside, but no such correlation was noted with gentamicin.

Under the following conditions, patients should be monitored for gentamicin blood levels:

(1) In patients with impaired renal function who are at a greater risk of developing nephrotoxicity, trough levels should be considered at three days, especially if either oliguria or volume depletion occurred during the first few days of the illness. An elevated trough level at this time would be a reason to reduce the dose of gentamicin or to change the interval of therapy. In other patients, elevated "trough" levels of either gentamicin (>2 μg/ml) or amikacin (>10 μg/ml) are associated with a 1 in 3 chance of the patient developing impaired renal function. Hence, levels should be of less value than a serum creatinine repeated at three days (which should be done in any case).

(2) Those patients receiving hemodialysis should have serum levels after the second administration of gentamicin. A variable extraction of gentamicin occurs with different hemodialysis coils so that adequate therapeutic levels must be individually determined (36).

(3) Peak levels should be performed in patients who continue to be febrile 3 days after therapy was initiated if a loading dose of less than 1.5 mg/Kg of body weight was administered. Noone has found a positive correlation between peak serum concentrations of 5 μg/ml and therapeutic efficacy in gram-negative septicemia (37). This group recommended that the dosage should be increased if peak levels fell below 5 μg/ml and should be preferably maintained at 8-12 μg/ml. In addition if the patient is febrile, blood cultures should be obtained since "break through" bacteremia at 3 days correlates with inadequate serum levels of gentamicin (which relates to an inadequate loading dose) (38). If the patient is afebrile and responding clinically, gentamicin levels are not indicated; in fact, many of these patients also have inadequate levels of gentamicin (38). There would be little reason for determining gentamicin blood levels toward the end of the course of treatment if the usual treatment course is 7-10 days. However, if gentamicin is to be administered for longer than 14 days, gentamicin levels can be drawn at 14 days to make sure excess levels are not being accumulated (Figure 5, p. 18).

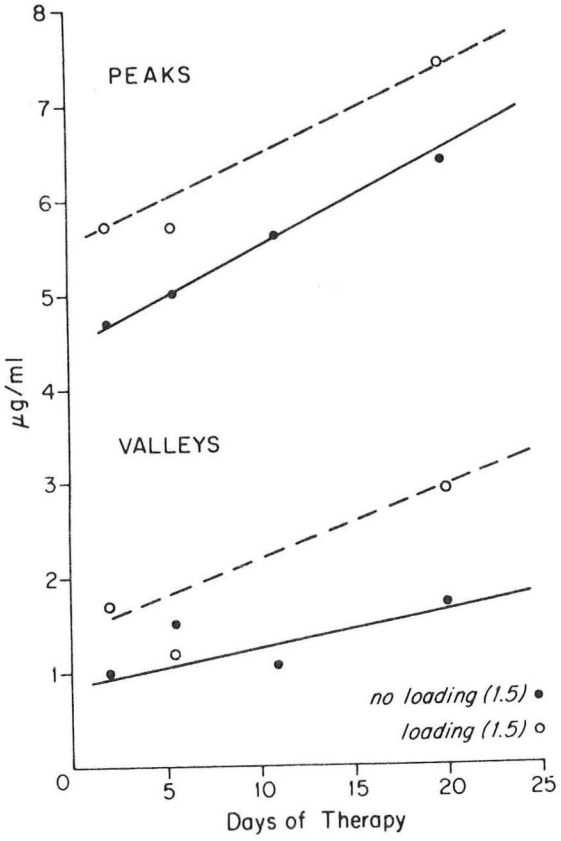


FIGURE 5: Relation of mean peak and valley serum concentrations in patients with normal serum creatinine receiving 1.5 mpk eight hourly to duration of therapy. Loading dose refers to an initial dose of 2 mpk (33).

(b) How should one approach persistent gram-negative bacteremia?

Case #3

J.H. was a 55 year old Latin American male, who presented in the fall of 1976 to the DVAH, with 1 month history of purpura over face and hands. He had noted easy bruisability, polyarthralgias and weight loss for two years. The lesions over the face and hands had black centers and purpuric margins. He had hepatomegaly, but no joint changes or lymphadenopathy. Laboratory abnormalities included a WBC of 2,400 with 91% polymorphonuclear leukocytes, elevated SGOT, hypergammaglobulinemia, positive latex fixation at 1:80 and ANA of 1:1280. He became lethargic and mentally confused and developed a small intestinal ileus. On the 6th hospital day, high dose steroids were begun for treatment of systemic lupus erythematosis with dramatic improvement in both the central nervous system and skin manifestations. On the 15th hospital day he spiked a temperature and blood cultures were positive for *Serratia marcescens*. He was begun on penicillin and

gentamicin as well as isoniazid for a positive PPD. The patient became afebrile; meanwhile steroids were tapered. However, 2 days after the gentamicin was discontinued, he again developed temperature and a painful left wrist. A culture of a joint aspirate was negative, but blood cultures were again positive. He again became afebrile on gentamicin but five days later, he was noted to have a slightly tender vein in forearm. Purulent fluid was aspirated which showed gram-negative rods and grew *Serratia marcescens*. The next day surgeons explored his arm and noted multiple purulent sites along a thrombosed vein. The vein was stripped, debrided and was left to drain openly. Blood cultures on gentamicin were negative, so on the 14th day of treatment gentamicin was discontinued. Eight days later, he was noted to have fever and a new nodule over the right forearm, which grew Serratia. Repeat blood cultures were again positive for *Serratia marcescens*. Antimicrobial susceptibility testing showed the organism was sensitive to carbenicillin, gentamicin, kanamycin and streptomycin. At this time, intravenous treatment with carbenicillin and gentamicin was begun. He achieved a serum killing power of 1:16 following the intravenous administration of the antibiotics with a trough (pre-antibiotic) of 1:4. His course was further complicated by the development of a lung abscess of uncertain etiology, a diastolic murmur at Erb's point and recurrent fever with tender IV sites. Sonogram of the abdomen, echocardiography of the heart valves and a gallium scan were all negative. His open draining sites continued to close as his steroids were tapered. He eventually became afebrile, gained weight and remained afebrile off antibiotics with negative cultures.

This patient demonstrates the problems in an immunosuppressed host who has persistent Serratia bacteremia related to phlebitis. He showed very few localizing signs but had repeatedly positive blood cultures when appropriate antibiotics were discontinued. Endocarditis was considered but never proved (39). He was eventually treated for 6 weeks with combination therapy, while monitoring serum bactericidal activity (40). Suppurative thrombophlebitis is a potentially lethal complication from indwelling venous cannulation retained for unusually prolonged periods (41). Suppurative phlebitis should be considered in a patient with inflammation at site of an intravenous catheter when:

(1) the signs of inflammation and size of the lesion are the same or increased after 24 hours of observation and local treatment
(2) the phlebitis extends above the elbow or
(3) the person is on immunosuppressive therapy or is leukopenic, in which case signs of inflammation may be minimal.

If any of these conditions are present, and if blood cultures are positive the site must be aspirated and explored surgically under sterile conditions. If purulence is detected, extensive debridement proximal to the venous site must be performed. Dramatic improvement in clinical course with defervescence within 24 hours will be noted in most cases if suppurative phlebitis is treated aggressively (41); otherwise, lethal consequences may ensue. In a recent careful survey of intravenous-catheter infections, 18% of catheters inserted demonstrated signs of inflammation,of which one-third had a positive culture (42). The majority of the organisms were *Staphylococcus epidermidis*, but a majority of cultures positive for *Staph aureus*, Candida or Klebsiella was associated

with septicemia. None had suppurative phlebitis. Inflammation at a site of intravenous catheter is probably the most common cause of fever occurring in a hospitalized person.Cultures should be done on subcutaneous portion of catheter when removed.

Persistent gram-negative bacteremia of which case #3 was an example is defined as a positive blood culture with the same organism repeatedly over a 7 day period or persistent bacteremia at least 3 days after institution of appropriate antibiotics (43). An undrained abscess, principally abdominal or perinephric, is the major cause of persistent gram-negative bacteremia (Table 10).

TABLE 10

Factors Responsible for Persistent Gram-Negative Bacteremia

| | Alabama (43) | | UCLA (38) | |
|---|---|---|---|---|
| | No. | % | No. | # |
| Total | 20 | - | 23 | - |
| Abscess | 9 | 45 | 7 | 30 |
| Intravascular | 8 | 40 | 0 | 0 |
| G-U | 4 | 20 | 4 | 17 |
| Pulmonary | 2 | 10 | 0 | |
| Leukopenia | - | - | 9 | 39 |
| Other | 5 | 5 | 3 | 13 |

Intravascular infections were also a common cause, with an infected intravenous catheter (as in our case) the primary site of infection although occasionally, they became secondarily infected following bacteremia. Anderson and her colleagues noted that late occurrences of "breakthrough" bacteremia occurred most frequently in patients with leukopenia due either to leukemia or aplastic anemia (38). In most cases these patients had adequate serum levels of antibiotics. Persistent gram negative bacteremia was noted in 5 of the 70 patients with gram-negative bacteremia at DVAH, January through June 1977 (Table 11, page 21).

A patient should be suspected of having persistent gram-negative bacteremia if fever persists after 3 days of antimicrobial therapy. Any clinical clues to infection must be diligently searched for. Since intraabdominal abscesses are such a common cause, gastrointestinal x-rays, abdominal sonography, liver spleen scan and intravenous pyelogram should be obtained. In our case of splenic abscess, the liver-spleen scan suggested a splenic abscess although arteriogram was done before he was explored. If the patient is immunosuppressed

TABLE 11

Persistent Gram-Negative Bacteremia

DVAH, January-June 1977

| Patient | Organism | Underlying disease | Therapy | Outcome |
|---|---|---|---|---|
| CG | *Serratia liquefaciens*<br>*Serratia marcescens*<br>*E. coli* | Carcinoma, ampulla of vater | Gentamicin<br>Chloramphenicol | Death |
| RW | *Klebsiella pneumoniae* | Alcoholic liver disease, ascites, osteomyelitis | Gentamicin<br>Cephalothin | Death |
| JH | *Serratia marcescens* | Systemic lupus erythematosis, phlebitis | Gentamicin<br>Carbenicillin | Cured |
| EH | *Serratia liquefaciens* | Post-op Whipple's for carcinoma-pancreas | Gentamicin<br>Carbenicillin | Death |
| JH | *E. coli* | Diabetes,<br>Sickle cell disease<br>Splenic abscess | Gentamicin<br>Chloramphenicol<br>(Splenectomy) | Cured |

or leukopenic, then adequate doses of appropriate antibiotics should be continued while work-up proceeds. Combination of agents which might be synergistic should be utilized if initial single-dose therapy fails.

Persistence of infection may indicate osteomyelitis, which in adults involves the lumbar, cervical or thoracic spine more commonly. The infection can be introduced following urinary tract infection, or can follow intra-abdominal infection with bacteremia (44). It begins initially with narrowing of the affected intravertebral space followed by increase in density of the adjacent proximal and distal vertebral bodies (45). Erosion of the vertebral plates, ballooning of the disc space with extension to involve the vertebral body, or less commonly, abscess formation occurs. Gram-negative bacilli should be considered if these changes occur after bacteremia. A bone scan will demonstrate increased uptake in the site of the lesion in virtually all the cases. Initial attempts at diagnosis can be made with aspiration of the disc space under fluoroscopy. Surgery may be required if aspiration is unsuccessful or if there is any evidence of a paraspinous abscess. Long term antimicrobial therapy is indicated. Osteomyelitis following gram-negative bacteremia is illustrated by the following case kindly provided by Dr. David Drennan from Methodist Hospital in Dallas.

Case #4

M.D. was a 77 year old black male who presented with a three day history of fever, chills, lower quadrant abdominal pain and occasional nausea and vomiting. In 1960 the patient was seen with cirrhosis and was treated for tuberculosis in the early 1960s. On physical, he was febrile, and had mild right lower tenderness. WBC was 75,000 with a left shift. Spinal tap and urine cultures were negative, but blood cultures grew out *Enterobacter aerogenes* and *Clostridium perfringens*. It was felt that the patient had an abdominal abscess, possibly secondary to a perforated diverticulum. He was treated with gentamicin and clindamycin and rapidly became afebrile. He remained afebrile after the antibiotics were stopped. The patient was doing very well and would not permit surgery proposed for a possible abscess. He returned to the hospital approximately two months later complaining of abdominal pain again with weight loss and weakness. At this time, on careful questioning, the patient's abdominal pain was attributed to referred pain from the back. Spine x-rays revealed a lytic lesion at the T-11 and T-12 level. A myelogram revealed a complete block at this level. Before the patient could be operated upon, his condition deteriorated with the onset of hypotension and a picture of septic shock. The patient responded to therapy with methicillin and gentamicin and treatment of shock. After he stabilized, a laminectomy was done. An inflammatory mass was found in the paravertebral areas. A decompressive laminectomy from T-10 through T-12 was done. Cultures from the inflammatory mass grew *Enterobacter* and he was then switched to tetracycline for long-term therapy.

Arthritis following gram-negative bacteremia is an uncommon entity, it is a very destructive process (46). Bacterial endocarditis also is a very uncommon event (47), very likely due to the failure of gram-negative bacilli to attach to the heart valve (48). Endocarditis has been reported in the immediate post-op period following prosthetic valve placement, although it is not certain that bacteremia with GNB actually represents endocarditis. In any persistent infection without an obvious site, long term therapy with a combination of drugs for 4-6 weeks should be considered.

## E. Control of Gram-Negative Bacillary Infections

### 1. Surveillance of gram-negative bacilli

Control of gram-negative bacterial infections remains the major thrust of any hospital infection control program. Aerobic gram-negative bacilli are the most common cause of hospital infections and hospital-associated bacteremias, whereas our traditional foe, *Staphylococcus aureus*, is of secondary numerical importance. Recent surveys of hospital-associated infections at the DVAH by our Infection Control Nurse, Miss Beverly Brown, have shown rates for the whole hospital and Surgical and Medical Service, to be comparable to rates in University hospitals surveyed by CDC recently. Her analysis has indicated that greater than 75% of all hospital associated infections and 63% of hospital-associated bacteremias were gram-negative organisms (Table 12,page 23). The principal site infected was the urinary tract, followed by post-operative wound infections.

TABLE 12

Bacteriology of Hospital-Associated Infection at DVAH

| | Hospital-Associated Infections | | Hospital-Associated Bacteremias |
|---|---|---|---|
| | April 1977 | August 1977 | April - August 1977 |
| Infection Rate per Admission | | | |
| - Hospital | 2.6% | 4.2% | 0.4% |
| - Surgery | 6.1% | 8.3% | 0.5% |
| - Medicine | 1.8% | 5.3% | 0.4% |
| Proportion of Infections | | | |
| - Gram-Negative Bacilli | 87% | 75% | 63% |
| - Gram-Positive | 13% | 25% | 30% |
| - Urinary Tract | 43% | 32% | 26% |
| - Wound | 28% | 27% | 8% |
| - Pulmonary | 12% | 18% | 15% |
| - IV | 4% | 3% | 19% |

Hospital-associated bacteremias were also most commonly secondary to urinary tract infection, but venous infections accounted for a larger proportion of bacteremias than of hospital-associated infections.

Control of hospital-associated infections requires continuous vigilance and care by hospital staff. A careful review of procedure-related bacteremias by McGowan and Infection Control Nurses at GMH, Atlanta, revealed that one-third of the episodes were associated with procedures for which proper technique could prevent infection (49). Variation from hospital guidelines occurred most commonly with bacteremias secondary to infected intravenous catheters and administration of hyperalimentation fluid. Review of seven hospital outbreaks of urinary tract infection caused by multiply-resistant gram-negative bacilli suggested transmission of the organisms from patient-to-patient on the hands of personnel (50). Secondary cases generally developed in patients with indwelling urinary catheters who resided in the same room or ward. Thus, the role of the Infection Control Nurse and the committee is to encourage good medical practices so that infections can be prevented and outbreaks controlled. Our major efforts at the VA have been twofold:

(1) to determine the problem areas by surveying the entire hospital periodically and reviewing all hospital-associated bacteremias and
(2) to control the spread of gentamicin-resistant organisms.

Our surveillance and educational program for gentamicin-resistant bacilli follows:

2. Surveillance and Control of Gentamicin-Resistant Organisms

a. Surveillance

Culture reports from the bacteriology lab were reviewed daily by the Infection Control Nurse for gentamicin-resistant gram negative bacilli. Those identified were grouped according to ward, site and species. No distinction was made as to whether these organisms represented colonization or actual infection. Charts of all patients harboring these organisms were carefully reviewed by the Infection Control Nurse in an effort to identify causative factors. To reduce the likelihood of transfer of these potentially dangerous organisms to other patients by the clinical staff, a "Body Discharge Precaution" notice was placed in the Nursing Care Plan.

Body Discharge Precautions

Sputum - Urine - Blood - Spinal Fluid - Feces

Wound Drainage

A. Purpose: To prevent possible transmission of multiply resistant organisms isolated from any of the above sites.

B. Comments: Strict handwashing with betadine soap before and after any contact with patient and/or secretion-contaminated articles, i.e.,

* emptying foley bag and doing perineal care
* caring for incontinent patient
* suctioning patient
* any dressing changes/wound care/burn care

1. No-touch technique
2. Dispose of soiled dressings and equipment in waxed paper bag

assisting any diagnostic procedure

* Please Use Gloves

Note: These precautions apply until it is proven that the patient is free of the infecting organism.

b. Data from surveys in April to August 1977 at the Dallas VA Hospital indicated that gentamicin-resistant organisms were most frequently isolated from the urinary tract (Fig. 6). Preliminary investigations suggested that long-term indwelling urinary catheters and urinary tract manipulation were the most important factors contributing to urinary colonization of patients by gentamicin-resistant bacilli.

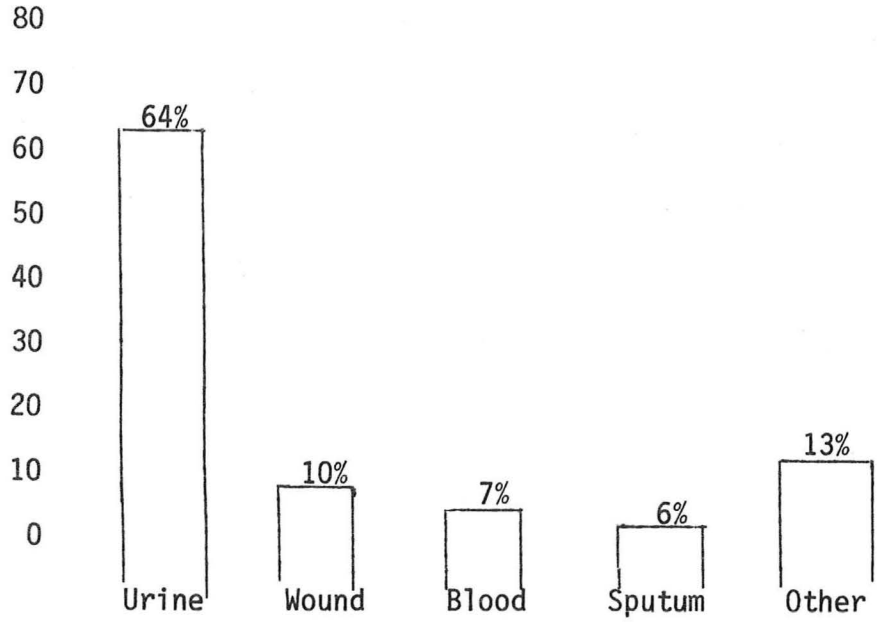


FIGURE 6: Frequency of isolation of gentamicin-resistant organism by site, April - August 1977.

c. Frequency of Organism

Pseudomonas spp. were the most common gentamicin-resistant bacilli although Proteus spp. esp. rettgeri, Klebsiella and Serratia spp. were also commonly resistant to gentamicin (Table 13).

TABLE 13

Frequency of Isolation of Gentamicin-Resistant Organisms by Species

| | % |
|---|---|
| Pseudomonas | 34 |
| Proteus | 19 |
| Klebsiella | 13 |
| Serratia | 12 |
| *E. coli* | 10 |
| Other | 12 |

d. Control Program

In April, six isolates of gentamicin-resistant Pseudomonas were obtained from patients residing on Urologic Ward 2S. All six patients had the organism identified in the urinary tract, had undergone surgery, and had had an indwelling urinary catheter at one time. The initial two cases were catheterized patients in beds next to each other in the post-op ward, which suggested that organisms from one patient may have been transferred to the second patient. In-service education was given to the staff on

this ward, following which a decrease was noted in the isolation of gentamicin-resistant gram negative bacilli from patients on this ward.

In May, five different patients on 4C had Pseudomonas isolates which were resistant to gentamicin. One isolate came from a stump wound, while the other four were from urine specimens. Again, it was discovered that two isolates were from patients occupying adjacent beds. Another patient with Pseudomonas isolated from urine had a foley catheter inserted at another hospital and was presumably colonized at that institution. All of the patients had manipulation of their urinary tracts during their hospitalization. Body discharge precautions were instituted in each of these cases to prevent spread of the organisms to other patients.

Surveillance from June on failed to demonstrate clustering of gentamicin-resistant organisms on any particular ward. Thus, the use of the precautions appeared to have had a positive effect in preventing spread of these organisms on particular wards. Control measures did not affect the overall rate of recovery, which varied from 9% in July to 14% in August.

Thus, gentamicin-resistant bacilli surveillance has been useful in uncovering infection control problems at an early stage. Continued surveillance will allow the Infection Control Nurse to institute control measures before the problem becomes widespread within the hospital. (This report was distributed as an Infection Control Committee quarterly report to the employees of the Dallas VA Hospital as an educational tool to increase their awareness of this problem). One consideration in the control of bacteremia secondary to urinary tract instrumentation would be to administer an antibiotic (such as gentamicin) prophylactically. This is not an accepted reason for prophylaxis (see list in 51) nor has it been successful in reducing bacteremia (52). Rather, the approach to the control of epidemics of urinary tract infection, especially due to multiply-resistant gram-negative bacilli, consists of education to emphasize hand-washing procedures and separation of patients with gentamicin-resistant strains with indwelling urinary catheters (50). If patients with catheters must share the same room, as in an intensive care setting, the patients and staff should be divided so that infected patients are cared for by separate staff from those who care for uninfected patients (52). This plan will minimize the opportunity for cross infection. We recommend hand washing with Betadine soap, although the CDC has noted that handwashing with soap and water may be sufficient (53).

3. Bacteremia Following Equipment

Bacteremia can also occur in hospitals as a consequence of breakdown in equipment or secondary to poor use of equipment (Table 14).

TABLE 14

Outbreaks of Bacteremia Following
Improper Use of Medical Devices

| Reference No. | Device | Improper use | Organism |
|---|---|---|---|
| 54 | Arterial Pressure Transducer | Reused disposable domes | *Serratia marcescens* |
| 55 | Hemodialysis Coil | Reuse of coils | *Pseudomonas aeruginosa* |
| 56 | Blood Collection Tubes | Back flow of blood | Serratia spp. |
| 57 | Arterial Catheters | Syringe contamination | Flavobacterium spp. |
| 58 | Intravenous Fluid Bottle Cap | Contaminated liner of cap | *Enterobacter agglomeran* |

Use of disposable equipment has had significant benefits in various areas. For example, in earlier times, catheters for cardiac catheterization were reused after soaking in antiseptic solution - Benzalkonium in which gram negative bacilli could grow. The frequency of fever and bacteremias was much higher following cardiac catheterization than it is presently with disposable catheters. However, attempts to reuse disposable items represents false economy as noted in reports on transducer domes, which became infected because they are altered by sterilization and can serve to introduce bacteria in blood stream (54). Contaminated syringes or blood tubes have been responsible for a number of outbreaks. In a recent survey in which Dr. Southern participated, a variable proportion of evacuated tubes for collecting blood were contaminated with a variety of microorganisms, with rates varying from 12% for red tubes to 38% for green tubes. Back flow of blood from these contaminated tubes can occur if the tourniquet is improperly used. This has been responsible for bacteremia with Serratia (56). It is, therefore, essential that the tourniquet be removed well before the blood stops flowing into the tube to prevent the risk of back flow. In another outbreak, syringe contamination of arterial catheters occurred when the syringes were cooled in contaminated ice before being used to obtain the arterial specimen. Various gram negative bacteria can contaminate ice machines, in this case flavobacterium, since they as Pseudomonas, grow much better at lower temperature (57). Prolonged use of any intravenous catheter leaves the patient at risk of developing bacteremia. This is especially true if bacteria are introduced from IV fluid as occurred when liners of caps of IV fluid bottles were contaminated with enterobacter species (58). This outbreak indicated that a number of factors are frequently responsible for increased chance of hospital-associated infection. Firstly, a technical advance led to the use of a liner which was commonly contaminated. Secondly, bacteria were more likely to be present in fluid if bottles had additives which had to be mixed before administration (or if bottle caps were hit on counter prior to opening). Thirdly, patients became infected if infused for long periods of time or if tubing was kept in place for excessive duration. This is one reason that it is recommended that IV tubing be replaced every 24 hours. Another common cause of septicemia following administration of fluid is candidemia in patients receiving total parenteral nutrition (59).

These organisms grow much better in hypertonic fluid than do bacteria. A significant factor responsible for septicemia during total parenteral nutrition is hypophosphatemia (60). Hence an important measure in such patients is to maintain the serum phosphate near normal.

F. Immunoprophylaxis of Gram Negative-Bacteremia

Considerable interest has been generated in an attempt to determine factors responsible for protection against gram-negative bacteremia. Unfortunately, multiple serotypes of each species have been responsible for bacteremia so immunization with type-specific antigen is not feasible. Hence, the major thrust has been to determine if the core portion of the lipopolysaccharide is an immunodeterminant which might lead to protective antibody. (Figure 3). Antigenic determinants of the core portion are shared by most gram-negative bacilli and a major advance was made when antiserum to the rough mutant of *Salmonella minnesota* (Re) strain was shown to react with all organisms in the family *Enterobacteriaceae* (21). Re consists solely of the KDO portion and lipid A (Figure 3). Antiserum to the Re strain was successful in inducing protection against infections with gram negative organisms (61). Braude and his group also reported protection in granulocytopenic animals against pseudomonas infection with antibody to core glycolipid (62). Antibody to core mutants do not induce opsonic (phagocytic) or bactericidal effects which does occur with type-specific antibody to the infecting bacteria (63). Thus, it has been theorized that protective antibodies act primarily as antitoxins (5). Young has also noted that pneumococcal vaccines produce protection against lethal bacteremia due to klebsiella or *E. coli* experimentally (5). He attributed this protection to shared capsular antigens which have been found between coliform bacteria and various serotypes of pneumococci.

It is not known if antibody to the core portion of the lipopolysaccharide would be protective in human infection. Indirect evidence favoring this has been accumulated in studies by McCabe who found that high titer antibody to the core glycolipid from the Re mutant correlated with a decreased frequency of shock and death (64). Studies also showed a decreased incidence of shock and death in individuals who had significant levels of specific IgG antibody to the lipopolysaccharide of the infecting organism (65). This protection would relate to opsonic activity since specific antibody in IgG class does enhance phagocytosis (66). Presence of antibody to lipid A did not correlate with protection against these complications of gram-negative bacteremia.

There have been no clinical trials of immunoprophylaxis with mutants of gram-negative bacilli nor of chemical preparations of the immunodeterminants of protection (hypothesized to be KDO). The Re mutants that have been moderately successful in experimental animals are toxic. Many patients would have to be immunized to show even modest improvements in case fatality rates. Significantly more study and confirmation of the protection in other species (as sub-human primates) are needed before clinical trials can be launched. Protection with antibody cannot be the exclusive reason for protection against complications in bacteremia. Four patients of the 70 in January-June 1977 with gram-negative bacteremia and cases #2 and 4 discussed

previously had significant infection and late complications of infection: shock and/or death, 3 to 4 weeks after bacteremia. In each of the cases, the later infection was with the same organism responsible for initial bacteremia. Hence these patients did not develop protective antibody (either type specific or core) even after previous exposure to large quantities of antigen (i.e. as with a blood stream infection). In case #2 high titer specific antibody was present. A recent study showed that nonspecific resistance to experimental infection with gram-negative bacilli and susceptibility to endotoxin shock was determined by a single autosomal dominant gene (67). It is possible that humans could vary in their response to gram-negative bacteremia and the likelihood of developing complications because of nonspecific resistance factors which are transmitted genetically.

Thus, multiple factors determine resistance or susceptibility to bacteremia with aerobic gram-negative bacteremia. The paramount defense resides with the polymorphonuclear leukocyte. Clinical trials of pseudomonas vaccines have not protected against bacteremic death in leukopenic patients (68). This cell does have enhanced activity in presence of specific antibody to the infecting organism. However, since each species has so many serotypes, specific antibody to the lipopolysaccharide of the infecting organism is not likely to be present until late in course of infection. If the person has been previously exposed to gram-negative bacilli (especially rough mutants with KDO only exposed) or to cross-reacting pneumococcal capsular antigens, then protection due to antibody to the core portion of endotoxin may be induced. Genetically-determined attributes may be an important factor that predisposes certain individuals to the complications of bacteremia. This likely accounts for the unusual susceptibility of certain patients to bacteremic shock. However, this can only occur if the person is exposed to these bacteria via natural causes or following complications from well-intended medical procedures. At present, the only preventable approach is to adhere to accepted standards as well as direct control programs at limiting certain high risk hospital-associated infections, such as those with gentamicin-resistant organisms.

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