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Clinical Implications of Positive Blood Cultures

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INTRODUCTION

The goals of medicine are accurate diagnosis, useful prognosis, and effective therapy. Toward each of these goals, clinicians find positive blood cultures to be invaluable. However, interpretation of blood cultures is fraught with subtleties and potential pitfalls. This review will focus primarily on the significance of positive blood cultures from a clinical perspective.

A HISTORICAL PERSPECTIVE

By 1940, the practice of obtaining blood for cultures from febrile patients had become well established (114). In early 1941, Chester S. Keefer of Boston summarized his extensive personal experience in a review entitled "The Clinical Significance of Bacteremia" (176). Later the same year, penicillin G was introduced into clinical practice. A perspective on changes brought about by antibiotics and other advances can be gained by comparing Keefer's data with those from any large present-day hospital.

Of Keefer's 479 cases of bacteremia, 250 were due to hemolytic streptococci, most of which were presumably group A streptococci (*Streptococcus pyogenes*). These bacteremias were associated with a 70% mortality rate. Keefer reported 122 cases of *Staphylococcus aureus* bacteremia and 54 cases of pneumococcal bacteremia, both of which were associated with 80% mortality rates. Gram-negative bacteremias accounted for only 11% of Keefer's cases. Most of these (40 of 53 bacteremias) were due to *Escherichia coli*, which was associated with a 35% mortality rate.

Today, group A streptococci account for fewer than 2% of positive blood cultures at most hospitals (48, 346). The death rates associated with gram-positive bacteremias have been reduced to about one-third their former levels. Although the impact of antibiotic therapy on gram-positive bacteremias was dramatic, an increased frequency and importance of gram-negative bacteremias soon became evident (111). At Boston City Hospital, for example, the number of bacteremias per 1,000 patient admissions nearly quadrupled (from 7.4 to 28.0) between 1935 and 1972, due in large measure to hospital-acquired gram-negative rod infections (222). The overall mortality rate among patients with gram-negative rod bacteremia was 39% in studies published between 1950 and 1970 (309). In a more recent series, 40% of all bacteremias were due to members of either the family *Enterobacteriaceae* or the family *Pseudomonadaceae*, and these bacteremias were associated with a 36% mortality rate (48, 55).

To some extent, the rising incidence of positive blood cultures may reflect the more frequent use of blood cultures by clinicians. Shown in Fig. 1 are data from Richland Memorial Hospital, Columbia, S.C., a 600-bed municipal teaching facility. Between 1977 and 1988, the number of patients admitted to this hospital each year remained relatively constant (23,106 in 1977; 22,847 in 1988). However, the number of blood cultures processed by the laboratory each year nearly tripled (from 5,692 to 14,384). The number of gram-negative bacteremias encountered each year rose modestly (from 170 to 242), but the number of gram-positive bacteremias rose markedly (from 412 to 934) and the number of fungemias rose dramatically (from 3 to 65). The resurgence of gram-positive bacteremias and the new importance of fungemias (149) are now widely appreciated.

By 1941, correlation of blood culture results with clinical and postmortem findings had provided a number of useful axioms. Keefer recognized the value of positive blood cultures, especially in patients without a clinically obvious localized infection. For instance, unexplained hemolytic streptococcal bacteremia raised the possibility of thrombophlebitis of the veins of the pelvis or the neck. Unexplained *S. aureus* bacteremia suggested either endocarditis or osteomyelitis "that has failed to produce localizing symptoms" (176). Pneumococcal bacteremia without pneumonia might arise from osteomyelitis, sinusitis, peritonitis, or endocarditis. *E. coli* bacteremia without an obvious source raised the possibility of biliary tract obstruction, multiple liver abscesses, or cirrhosis. In the latter respect, Keefer anticipated the diverse syndromes of spontaneous bacterial peritonitis (77). Today, an enormous body of literature attests to the relevance of such correlations.

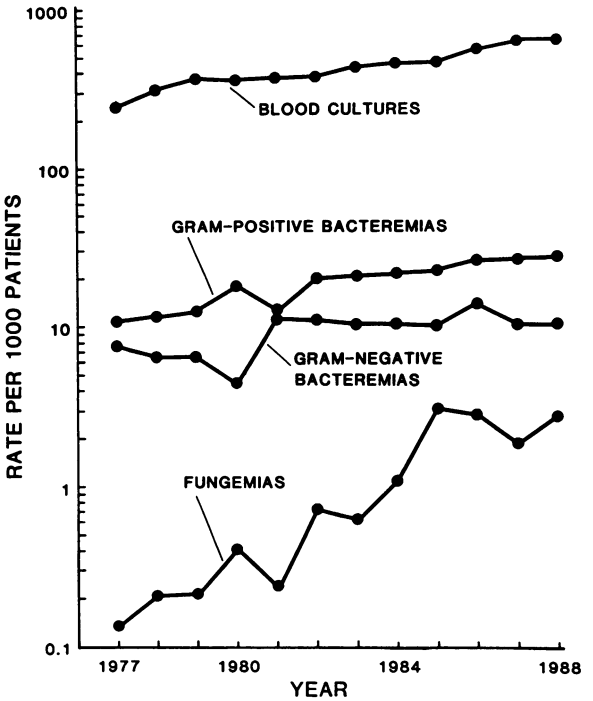

FIG. 1. Relationship between number of blood cultures processed and documentation of bacteremia and fungemia at a municipal teaching hospital, 1977–1988 (semilogarithmic scale).

Because microorganisms other than bacteria were seldom isolated from blood cultures in the pre-antibiotic era, it was appropriate for Keefer to equate "positive blood culture" with "bacteremia." The rising frequency of fungal blood isolates explains a recent trend to speak of "bacteremia and fungemia" (353). However, "bacteremia and fungemia" does not entirely suffice, since other kinds of microorganisms are being identified in blood cultures, especially as a result of the acquired immunodeficiency syndrome (AIDS). It is significant that, while a 1973 monograph was entitled *Bacteremia* (303), a 1988 monograph is entitled *Bloodstream Infections* (314).

The term *bloodstream infections* also has a limitation: the mere presence of microorganisms in blood denotes neither active multiplication nor harmful consequences. In other words, the presence of microorganisms in blood can be "incidental" (123). "Sepsis" refers to the harmful effects of microorganisms or their products in blood or in tissues but, in contrast to "septicemia," does not imply that blood cultures are positive (Fig. 2). In this review, bacteremia and

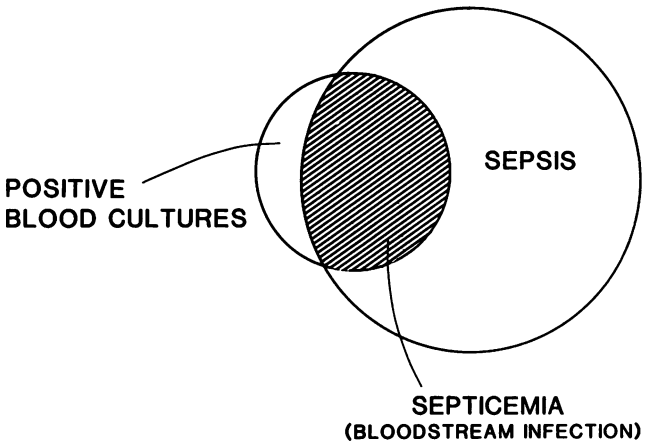

FIG. 2. Relationships among positive blood cultures, sepsis, and septicemia (bloodstream infection).

fungemia will be used to denote positive blood cultures, while septicemia and bloodstream infection will be used interchangeably. No attempt will be made to review viremia and parasitemia. After reviewing the general significance of positive blood cultures, I shall focus on specific bacteremias and fungemias, with emphasis on the recent literature.

INTERPRETATION OF BLOOD CULTURES

False-Positive Versus True-Positive Blood Cultures

Confronted with a positive blood culture, the clinician must judge its significance from several points of view (Table 1). Foremost among these is whether the result is "true positive" or "false positive" (pseudobacteremia). Contamination can arise at any point between the manufacture of the blood culture system and the final subculture. Useful guidelines include the microorganism's reputation for pathogenicity, its pattern of growth, and the extent to which the result "fits" the other clinical findings.

Weinstein et al. scrutinized the clinical and microbiologic data from a large series of blood isolates to determine "true septicemia" as opposed to "contamination" (343, 346). In general, gram-positive bacteria were more likely to be contaminants than were gram-negative bacteria. Frequent contaminants included coagulase-negative staphylococci (94%), *Bacillus* species (94%), and *Corynebacterium* species (79%). The problem of "endemic staphylococcal pseudobacteremia" (315) has become familiar at most hospitals. That 48% of viridans streptococcal isolates and 25% of *S. aureus* isolates were contaminants is somewhat disturbing, since isolation of these bacteria from blood cultures without an obvious source always raises the possibility of endocarditis. Enterococci were contaminants in only 13% of instances, while pneumococci and group B streptococci were judged never to be contaminants.

Although Weinstein et al. considered 2 of 13 *Enterobacter aerogenes* isolates to be contaminants, the other gram-negative rods in their series were true pathogens in at least 93% of instances. Hence, the clinician must usually attach credence to gram-negative-rod isolates from blood cultures. However, epidemics of pseudobacteremia are especially likely to involve gram-negative rods (D. G. Maki, Editorial, Arch. Intern. Med. **140**:26–28, 1980). Recent examples include *Pseudomonas cepacia* pseudobacteremia traced to contaminated povidone-iodine solution (27) and *Ewingella americana* pseudobacteremia associated with filling nonsterile tubes prior to filling blood culture bottles with blood from the same venipuncture (225, 226). Laboratory personnel should be alert to the possibility that any unusual increase in the frequency with which a gram-negative microorganism is isolated from blood cultures might represent a pseudoepidemic. Failure to do so can expose many patients to unnecessary antimicrobial therapy.

Traditionally, clinicians have regarded "growth in more than one bottle" or "growth in more than one culture set" as evidence of a true-positive culture. The number of positive sets, each representing a separate venipuncture, out of the total number of sets obtained is a more important criterion than the number of positive bottles. At some centers, determining the number of colony-forming units (CFU) per milliliter of blood by pour plates was used as another guideline. Newer systems, notably that based on lysis-centrifugation, now make quantitative blood cultures a less cumbersome procedure. It seems likely that the intensity of growth and also the rapidity of growth will replace growth in more than one bottle to an increasing extent.

Duration

It is customary to regard "true" bacteremia or fungemia as transient, intermittent, or sustained (continuous) based on whether a few, some, or all of a series of blood cultures are (or would be expected to be) positive. Transient bacteremia or fungemia, a frequent result of the traumas of everyday life as well as medical and dental procedures, assumes importance because of its role in pathogenesis. Prior to removal by the body's normal clearance mechanisms (26), the circulating microorganisms may find a haven in a damaged tissue or organ, that is, a locus minoris resistentiae. Endocarditis, the best-known example, has stimulated numerous investigators to define the incidence of transient bacteremia or fungemia after various procedures (16, 36, 93, 106, 201, 285). Transient bacteremia or fungemia also explains most cases of hematogenous osteomyelitis, many infections related to foreign implants of all types, and at least some infections of heavily traumatized tissues, hematomas, or necrotic tumors. Among critically ill patients receiving intensive care, transient bacteremias or fungemias arising spontaneously from the gastrointestinal tract cause many such infections (215).

Intermittent bacteremia or fungemia usually reflects established infection extrinsic to the bloodstream. In general, localized infections that give rise to bacteremia or fungemia are associated with greater mortality rates compared with localized infections without positive blood cultures (218). Serial quantitative blood cultures typically document wide

TABLE 1. Parameters for evaluating positive blood cultures

Parameter	Considerations
Veracity	True-positive vs false-positive
Duration	Transient vs intermittent vs continuous
Pattern of occurrence	Single episode vs persistent vs recurrent
Clinical severity	Inconsequential vs life threatening
Intensity (CFU/ml)	High grade vs low grade
Lethality	Crude mortality vs attributable mortality
Site of acquisition	Community acquired vs nosocomial
Source	Primary vs secondary
No. of microorganisms	Polymicrobial vs unimicrobial

fluctuations in the intensity of the bacteremia or fungemia, as expressed by the number of CFU per milliliter of blood. Such fluctuations provide the rationale for obtaining multiple specimens by separate venipunctures spaced over time, as opposed to obtaining a large volume of blood from a single venipuncture (338). Sustained bacteremia or fungemia is the hallmark of intravascular infections such as endocarditis, suppurative thrombophlebitis, endarteritis, mycotic aneurysm, and infected arteriovenous fistula. Not only are all blood cultures positive, but also the intensity of bacteremia or fungemia (CFU per milliliter) tends to be remarkably even. Sustained bacteremia also occurs in the early stages of brucellosis and typhoid fever and seems to be an asymptomatic feature of lepromatous leprosy (97).

Several adjectives descriptive of the course of bloodstream infection over time should be mentioned briefly. Persistent bacteremia or fungemia denotes a failure to clear microorganisms from the blood, whereas recurrent bacteremia or fungemia indicates two or more episodes separated by an infection-free interval. Recurrent bacteremia or fungemia typically occurs in chronically or seriously ill hospitalized patients and has a strong association with underlying malignancy (240). Anderson et al. (9) introduced the term *breakthrough bacteremia* for persistent or recurrent bacteremias during therapy with antibiotics to which the isolated pathogens were susceptible in vitro. Plasma antibiotic concentrations were found to be subinhibitory at the time the positive blood cultures were obtained in one-half of instances. These investigators concluded that breakthrough bacteremia early during the course of therapy was often associated with subinhibitory antibiotic levels. However, late breakthrough bacteremias were typically associated with inadequate drainage of purulent collections or with impaired host defenses (9). Laboratory personnel might suspect persistent, recurrent, or breakthrough bacteremia, especially when a microorganism previously isolated from the patient displays a different colonial morphology or a different pattern of antimicrobial susceptibility or both (283).

Clinical Severity and Intensity

The consequences of bloodstream infection have an impact on every organ system (148). A variety of laboratory parameters correlate with the presence and severity of septicemia (1, 42, 151, 313, 340) but do not replace the bedside assessment of "toxicity." Findings suggesting toxicity include hypotension, lactic acidosis, hypoxemia, oliguria, confusion, disseminated intravascular coagulation, gastrointestinal bleeding, disturbances of metabolism, and subtle skin lesions (148, 182). The most severe manifestations can be summarized by one word: shock.

More than a century ago, the surgeon Samuel D. Gross defined shock as "a rude unhinging of the machinery of life." Recent investigations of the molecular basis of septic shock underscore the aptness of this definition. A catalog of possible physiologic mediators of septic shock now includes components of the intrinsic coagulation, complement, fibrinolysis, and kinin systems; catecholamines, leukotrienes, histamine, serotonin, acetylcholine, and glucocorticoids; prostaglandins; endorphins; and a variety of products released or secreted by phagocytic cells. The latter include lysosomal enzymes, interleukin-1, interferons, and cachectin (148, 218). Recent research centers especially around the macrophage product cachectin, which seems capable of reproducing the septic shock syndrome experimentally (231).

A number of microbial components and products appear capable of setting these physiologic mediators in motion. Earlier work centered especially around the biologically active lipid A moiety of cell wall lipopolysaccharide, or endotoxin. The presence of this moiety in many gram-negative bacteria, but not in gram-positive bacteria, apparently accounts for the unique occurrence of hypotension early in the course of bacteremia due to gram-negative microorganisms (32). However, after septicemia has become well established, it appears that the nature of the causative microorganism has less significance (355). Septic shock can be defined as inadequate tissue perfusion with cell death due to peripheral circulatory failure resulting from an infection (148). The likelihood that it will occur is determined by the extent of any localized infection, the virulence of the infecting microorganism(s), the patient's underlying condition, and the intensity of bacteremia or fungemia.

In general, gram-positive bacteremias assume greater intensities (CFU per milliliter) than do gram-negative bacteremias. Similarly, bacteremias in infants and children tend to assume higher magnitudes compared with bacteremias in adults (314). After allowance has been made for these microorganism- and age-related trends, it appears that the intensity of bacteremia correlates in a general way with its clinical severity (92, 99, 186, 192, 214, 352). Recently, it has been suggested that serial colony counts provide a useful guide to the response to therapy (354). When bacteremia or fungemia becomes unusually severe, large numbers of microorganisms are sometimes seen in random peripheral blood smears; this occurs especially in asplenic patients and in overwhelming opportunistic infections (46, 128). Such infections are usually rapidly fatal, although survivors have been reported (193).

EPIDEMIOLOGY

Frequency

In 1969, Martin suggested that a national bacteremia registry be maintained "to collect and analyze bacteremia in the United States in an ongoing, comprehensive, systematic fashion" (C. M. Martin, Editorial, J. Infect. Dis. **120:** 495–496, 1969). Recent investigators continue to make this plea with regard to hospital-acquired bacteremias and fungemias (143, 348). Pointing out that the death rate attributed to septicemia increased 61% between 1979 and 1984, Wenzel has argued that bloodstream infections should be "a new vital statistic" (348). The question arises whether this trend reflects, at least in part, the more frequent obtaining of blood cultures in today's medical practice. In general, infectious diseases are being recognized more often than was formerly the case because of heavier utilization of laboratory services (142). Another factor is the refinement of blood culture techniques.

Various estimates of the frequency of bacteremia have been made from time to time. By one estimate, 169,000 community-acquired bacteremias and 176,000 hospital-acquired bacteremias occur in the United States each year (48). The frequency with which bacteremia and fungemia are recognized seems to be increasing at hospitals around the world (166, 173, 327). In the United States, a consistent trend at this time seems to be the rising incidence of gram-positive bacteremias and fungemias. At selected hospitals in Virginia during 1978 to 1984, for example, coagulase-negative staphylococcal bacteremias increased by 3-fold and fungemias increased by 15-fold (235). On balance,

the ever-rising incidence of nosocomial bloodstream infection seems to be an unfortunate by-product of medical progress, one unlikely to be reversed in the near future.

Lethality

Despite the availability of effective antimicrobial agents against nearly all blood isolates, the mortality (or case/fatality ratio) among patients with documented bacteremia or fungemia remains high. In a study from Columbia, S.C., based on 2,978 episodes of bacteremia at four hospitals, the 30% mortality among patients with bacteremia represented a 12-fold excess over the mortality among patients without bacteremia (48). In a study from Denver, Colo., based on 500 episodes of bacteremia and fungemia at two hospitals, a 42% mortality was observed (343, 346). A criticism of most of the older studies in the literature is that "death directly due to infection" was not distinguished from "death due to all causes" (309). Using quite different methods, the South Carolina and Colorado investigators, respectively, determined that 49 and 46% of deaths among patients with positive blood cultures were directly due to infection. Thus, about one-half of the deaths among patients with bacteremia or fungemia seem to be attributable to the infection. It seems best to speak alternatively of crude mortality or attributable mortality.

Another approach to the lethality of bloodstream infection is to analyze when death occurred in relation to the day on which the first positive blood cultures were obtained (that is, in relation to the day on which these specimens were obtained from the patient). Discrepancies between crude mortality and attributable mortality soon become apparent. Certain microorganisms, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*, tend to kill quickly, so that deaths generally occur soon after the onset of bacteremia. Other microorganisms, in one study including enterococci, *Serratia marcescens*, and *Bacteroides fragilis*, are typically associated with late deaths (48). In many instances, the latter microorganisms may be markers of serious illness or may indicate disease with surgical implications, such as perforation of the bowel (56, 58). In summary, certain bacteremias and fungemias tend to cause death, whereas others tend to be associated with death. These distinctions can, however, be difficult to resolve in individual cases. At postmortem examination, cultures of the spleen may be helpful as a guide to whether bloodstream infection actually caused death (275). Data obtained from such studies are of more than academic significance, since clinicians must determine which bacteremias and fungemias require aggressive antimicrobial therapy.

Host Factors

The increased mortality due to bloodstream infections at the extremes of life is well known (348). Among newborn infants, bacteremias due to *E. coli*, group B streptococci, and *Listeria monocytogenes* often lead to meningitis, perhaps because of the immaturity of the blood-brain barrier. In neonatal intensive care units, coagulase-negative staphylococcal bacteremias are of increasing concern (95). After the first year of life, *H. influenzae* becomes the major bacterial nemesis of childhood (224), but death due to hospital-acquired bloodstream infection is uncommon (57). Among the elderly, bloodstream infections are not only associated with increased mortality but are also difficult to recognize, due in part to the phenomenon of "afebrile bacteremia" (125). Several studies suggest that failure to mount a febrile response to septicemia correlates with the likelihood of death (125, 342). Changing mental status can be a subtle clue to the presence of septicemia in elderly patients. Prompt recognition of this event, followed by effective antimicrobial therapy, improves survival (230).

In 1962, McCabe and Jackson established severity of underlying disease as a key determinant of the risk of death due to gram-negative bacteremia (217). Bacteremic patients with either "rapidly fatal" or "ultimately fatal" diseases were much more likely to die than patients with "nonfatal" underlying conditions. The continued high-level concern about septicemia in granulocytopenic cancer patients confirms the validity of rapidly fatal disease as a determinant of outcome (294). However, the changed prognosis of many ultimately fatal conditions since 1962 has prompted the study of alternatives based on disease coding systems (116) or physiology (35). Nevertheless, the McCabe-Jackson criteria remain useful (48). In patients with cirrhosis (an ultimately fatal disease), for example, recent studies suggest that bacteremia occurs five to seven times more often than in the general population, portends a poor prognosis for the underlying liver disease, and carries some risk of endocarditis (4, 134, 135, 301).

Correlations between specific host defense deficiencies and patterns of infection are now well established. Familiar examples include the predisposition of B-lymphocyte deficiency to pneumococcal, *H. influenzae*, and neisserial infections; that of T-lymphocyte deficiency to mycobacterial, *Nocardia*, *Listeria*, *Salmonella*, *Legionella*, *Pneumocystis carinii*, and *Toxoplasma gondii* infection; and that of granulocytopenia to gram-negative rod, staphylococcal, *Corynebacterium*, yeast, and *Aspergillus* infections (255). Patients with diabetes mellitus are more likely to experience bacteremia compared with the general population, although the mortality rate per episode is not increased (59). Patients with sickle cell anemia are more likely to experience *E. coli* bacteremia in addition to the better-known associations, *Salmonella* and pneumococcal bloodstream infections (262). Many other examples can be cited.

Conversely, certain bloodstream infections have a diagnostic usefulness in that they actually suggest an underlying disorder. Persons who have experienced more than one episode of neisserial bacteremia (*Neisseria gonorrhoeae* or *N. meningitidis* or both) should be screened for homozygous deficiency of the sixth, seventh, or eighth component of complement. Of 24 patients with such a deficiency who had been reported through 1979, 13 had experienced at least one episode (and usually two or more) of neisserial bacteremia (254). Pneumococcal septicemia can be the presenting manifestation of multiple myeloma (18), or (especially if extremely intense) it may indicate congenital absence or acquired atrophy of the spleen (328). While the association of *Streptococcus bovis* bacteremia with neoplasms of the colon has been appreciated for more than a decade, it was recently pointed out that the bacteremia can predate the tumor by many years (P. Z. Honberg and E. Gutschik, Letter, Lancet i:163–164, 1987). Community-acquired bacteremia due to methicillin-resistant strains of *S. aureus* raises the possibility of intravenous drug abuse (82, 84, 288). More recently, recurrent or persistent *Salmonella* bacteremia has been incorporated into the case definition of AIDS. However, about two-thirds of bacteremias associated with AIDS are caused by microorganisms other than those classically associated with deficient T-lymphocyte function (351), illustrat-

ing that exceptions to such well-known host-parasite relationships are frequent.

THE CLINICAL SETTING

Nosocomial Versus Community Acquired

Nosocomial (hospital-acquired) bloodstream infection is generally defined by onset on or after the third day of hospitalization. Among the common pathogenic bacteria, both *S. aureus* and *E. coli* are frequent causes of both community-acquired and nosocomial bacteremia. However, most of the other common microorganisms encountered in blood cultures tend to belong to one or the other camp. The virulent encapsulated bacteria such as *Streptococcus pneumoniae*, *H. influenzae*, and *N. meningitidis* typically cause community-acquired rather than nosocomial infection. Opportunistic pathogens such as *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Candida albicans* typically cause nosocomial bloodstream infection. Exceptions are common, and patterns change. For example, pneumococcal bacteremia is being increasingly recognized as a nosocomial event (5, 69). The recent literature focuses especially on the problem of nosocomial bloodstream infection in intensive care units (83, 113). Case-controlled studies of hospitalized patients indicate that nosocomial septicemia increases the crude mortality rate by 4- to 14-fold. Among survivors, both the duration and the cost of hospitalization are substantially greater compared with patients without bloodstream infection (279, 307).

Most nosocomial septicemias are endemic; that is, they occur at rather predictable rates and can be regarded as part and parcel of the risk of hospitalization. Recent trends in the United States include the resurgence of *S. aureus* and the rising prominence of coagulase-negative staphylococci, enterococci, anaerobic bacteria, and fungi as causes of endemic nosocomial bloodstream infection (221). It is disappointing that only about one-fourth of these infections appear to be preventable by current techniques (223). The frequent isolation of such bacteria as *Pseudomonas cepacia*, *Pseudomonas maltophilia*, *Flavobacterium* species, and *Enterobacter agglomerans* by the laboratory suggests the possibility of an epidemic that might be due to contamination of intravenous infusion systems (206). An especially well-known nationwide epidemic resulted in the recall of one manufacturer's intravenous fluids on 22 March 1971 (208). Recognition of that epidemic would almost certainly have been delayed had a common microorganism such as *E. coli* been involved, rather than two unusual species. However, even *E. coli* can cause transfusion-related septicemia (11). Determination of the rates of nosocomial bacteremia and fungemia is easily accomplished and provides a background for early recognition of such epidemics (41).

Nosocomial septicemias due to *Pseudomonas aeruginosa* or *Candida* species are correlated with especially high crude mortality rates. Other factors that unfavorably affect mortality include advanced age, severe underlying disease, shock, an intraabdominal or lower respiratory tract origin for the bloodstream infection, and the absence of an identifiable source of origin (124, 232, 343). Among critically ill patients, the association of bloodstream infection with the adult respiratory distress syndrome and multiple organ failure carries especially high mortality. Bell et al. (23) determined that all such patients in whom a source of septicemia could be identified survived hospitalization, whereas all patients without an identified source died. Postmortem examinations revealed the peritoneal cavity to have been the site of the overlooked infection in seven of nine instances (23). Especially in intensive care units, heavy usage of one or another antibiotic correlates with the emergence of drug-resistant nosocomial pathogens (49). Such strains can also be spread from one hospital to another within a community, the hands of medical personnel serving as a mode of spread (289).

Primary Versus Secondary

Primary bacteremia or fungemia, a term popularized by the Centers for Disease Control National Nosocomial Infections Study, refers to cases without an identifiable source. The sources of secondary bacteremias or fungemias usually correlate with specific pathogens according to the body's normal microbial flora or according to the microbial adherence phenomenon. Insights into the molecular basis of this phenomenon explain such well-known associations as *Streptococcus pneumoniae* with respiratory tract infections, *E. coli* with pyelonephritis, and *N. gonorrhoeae* with salpingitis. It continues to be useful to monitor, from time to time, the microorganisms associated with various clinical syndromes. For example, *E. coli* continues to be the most common cause of secondary bacteremia arising from the biliary tract (295), while *B. fragilis* should be remembered along with gram-negative rods and staphylococci in patients with decubitus ulcers (45). Knowledge of the source of origin of bloodstream infection is also useful for prognosis. At present, attributable mortality appears to be low among patients with bacteremic urinary tract infection unless advanced age or severe underlying disease is present (53, 54). However, attributable mortality for bacteremic pneumonia remains high, especially when the pneumonia is hospital acquired (52, 339). Recognition of the source of infection is also predictive, to some extent, of whether blood cultures are likely to be positive. For instance, only 2 of 50 adults with acute cellulitis were found to have positive blood cultures (159), thus raising the question of whether blood cultures are cost-effective in this setting.

While the term *primary bacteremia* or *fungemia* is usually applied to nosocomial infections, the origin of community-acquired bloodstream infections is also frequently obscure. This is especially the case early in the course of infection. A large literature deals with "occult bacteremia" (alternatively, "walk-in bacteremia") in children between 3 months and 3 years of age who present with fever but no localizing signs of infection. These bacteremias are most often due to *Streptococcus pneumoniae* or *H. influenzae* and are occasionally due to *N. meningitidis* or *Salmonella* serotypes; prognosis is generally good, but serious complications can occur (65, 167). In a recent study of adult outpatients who presented with fever unaccompanied by localizing signs of infection, it was determined that patients with positive blood cultures usually had two or more of the following: age of >50 years, diabetes mellitus, leukocyte count of 15,000/mm^3 or greater, and a sedimentation rate of at least 30 mm/h (228). Keefer's dictum that community-acquired *S. aureus* or viridans streptococcal bacteremia without an obvious source should prompt the consideration of endocarditis (176) still holds.

Vascular access devices are considered to be the most common sources of primary nosocomial septicemias, and the magnitude of this problem is increasing. The risk appears to be especially great with triple-lumen and pulmonary artery catheters and is enhanced by the presence of severe illness, diabetes mellitus, hyperalimentation, and hemodial-

ysis (39, 155, 212). Confronted by the problem of sepsis in a patient with such a catheter, the clinician must determine whether the catheter is infected and must decide whether to remove the catheter. Catheters that have been removed should be evaluated by the semiquantitative culture method introduced by Maki et al. (209) or by its recent modifications (74, 75, 78, 360).

Whether it is valid to obtain blood through the catheter in instances of suspected septicemia is controversial. In one study in which matched cultures were obtained by venipuncture and through the catheter, 23 of 25 isolates obtained only from the catheter specimen were judged to have been contaminants (61). However, quantitative cultures of blood drawn through the catheter seems to be of definite value for evaluation of suspected catheter-related septicemia. Various investigators have concluded that a 5- or 10-fold-greater intensity of bacteremia or fungemia (CFU per milliliter) in the "through the catheter" specimen compared with the peripheral venipuncture specimen implicates the catheter as the source (24, 236, 263). Recent data suggest that removal of the catheter is not always required, even when the catheter has been implicated by such cultures. However, removal of the catheter is usually necessary in catheter tunnel infections (24). Catheter-related septicemias are often both intense and sustained. Hence, metastatic infections can occur in any organ or tissue. An especially feared complication is nosocomial endocarditis, which can be difficult to recognize and which carries a high mortality (323).

Unimicrobial Versus Polymicrobial

Polymicrobial, as opposed to unimicrobial, bacteremia or fungemia refers to the isolation of more than one microorganism from cultures. Weinstein et al. demonstrated that polymicrobial episodes were especially likely to be hospital acquired, to arise from the bowel or from multiple locations, and to be associated with tumors or other serious underlying diseases. Microorganisms especially likely to be associated with polymicrobial septicemia included members of the *Enterobacteriaceae*, members of the *Pseudomonadaceae*, nongroup A streptococci, and anaerobes. The overall death rate among patients with polymicrobial bacteremia was twofold greater compared with patients with unimicrobial bacteremia. The risk of death was increased by advanced age, blunted febrile response, primary focus of infection in the bowel or the lower respiratory tract, associated abscess, or an occult unidentified infection (345). In another report, the risk of death among patients with polymicrobial bacteremia was similar to that among those with unimicrobial bacteremia (266). However, there is little doubt that the frequency of polymicrobial bacteremia is increasing, especially among cancer patients (104). The isolation of more than one fungal species from blood cultures (polymicrobial fungemia) has also become more common (140).

The extent to which documentation of all microorganisms in blood cultures is necessary, however, has not been fully determined. On the one hand, Weinstein et al. concluded that failure to provide adequate antimicrobial therapy against all of the isolates correlated with unfavorable outcomes (345). On the other hand, Spencer and Nicol concluded that detection of additional isolates by repeated subculture suggested changes in the therapy of only 6 of 71 patients (306).

In general, infections contiguous to body surfaces containing a heavy "normal flora" should be assumed to be polymicrobial and treated accordingly. Common examples include intraabdominal and pelvic infections, traumatic wound infections, and necrotizing soft-tissue infections. On the other hand, infections occurring in normally sterile body fluids, tissues, or cavities are more frequently due to a single microorganism. Hence, greater confidence can be placed in the likelihood that a given laboratory isolate is, in fact, the cause of infection. Infections that are usually unimicrobial include endocarditis, meningitis, pyelonephritis, hematogenous osteomyelitis, septic arthritis, and pneumonia not due to the aspiration of "mouth flora." However, exceptions occur. For instance, a recent report documented three cases of polymicrobial bacteremic pneumonia due to the combination of *Streptococcus pneumoniae* and *Staphylococcus aureus* (127). Such cases illustrate that refinement in culture techniques do not replace the need for microscopic examination of specimens by using Gram or other stains.

SPECIFIC MICROORGANISMS

An extensive and growing body of literature addresses the clinical implications of the more common bacteremias and fungemias. Many of the less common bacteremias and fungemias are also associated with distinctive syndromes (Table 2). Here, emphasis will be placed on the more salient and clinically relevant observations from the recent literature.

Aerobic Gram-Positive Bacteria

Staphylococcus aureus. The rising incidence of *S. aureus* bacteremia may be due in part to the improved efficiency of newer blood culture systems (336). However, the spread of methicillin-resistant (beta-lactam-resistant) strains and the appearance of the toxic shock syndrome attest to the versatility of "the persistent pathogen" (292). Community-acquired cases can be difficult to recognize in their early stages, resembling an influenzalike illness or even Rocky Mountain spotted fever (233). However, the majority of cases are now nosocomial (50, 241). At present, *S. aureus* bacteremia is associated with a 24 to 41% crude mortality and an 11 to 20% attributable mortality (241). The age distribution of patients with *S. aureus* bacteremia tends to be biphasic, with one peak in the third decade of life and a second peak in the seventh decade of life. Mortality is especially high among the elderly (50). Immunocompromised patients whose bacteremias exceed 100 CFU/ml are at high risk of metastatic abscesses in various tissues and organs (352).

Recent estimates suggest that 5 to 20% of patients with *S. aureus* bacteremia have endocarditis, which requires prolonged antimicrobial therapy for cure (241). Unfortunately, there is no definitive method for excluding the presence of endocarditis. *S. aureus* frequently appears in the urine of patients with *S. aureus* bacteremia irrespective of the source of bacteremia (194). The optimum management of nosocomial *S. aureus* bacteremia related to vascular access devices has been controversial. Most of the experience has been that endocarditis is uncommon, provided that infected catheters are removed and that the patients have no risk factors for endocarditis, such as valvular heart disease or prosthetic heart valves (101, 239). Still, patients who receive short-course antibiotic therapy must be followed for the possibility of relapse (101). The premise that patients who have endocarditis or other deep-seated infections will mount significant antibody responses to teichoic acid and other *S. aureus* components or products continues to be studied as a basis for making this distinction (333).

TABLE 2. Examples of syndromes associated with less common bacteremias and fungemias

Microorganism(s)	Associations[a]
Streptococcus bovis	Carcinoma or villous adenoma of the colon
Group G streptococci	Acute endocarditis; malignancy or alcoholism
Corynebacterium JK	Central vascular access line infections in granulocytopenic cancer patients
Erysipelothrix rhusiopathiae	Aortic valve endocarditis in males with history of exposure to animals
Haemophilus parainfluenzae, *H. aphrophilus*, *Cardiobacterium hominis*, and *Actinobacillus actinomycetemcomitans*	Endocarditis with embolic occlusion of major arteries
Providencia stuartii	Urinary tract obstruction or paraplegia in elderly men
Citrobacter freundii	Disease of the gallbladder or small intestines
Pseudomonas cepacia	Contaminated fluids or equipment; nosocomial outbreaks
Aeromonas hydrophila	Exposure to fresh water; malignancy or cirrhosis
Pasteurella multocida	Cat bites; malignancy or cirrhosis
Vibrio vulnificus	Ingestion of raw oysters; males with cirrhosis
Campylobacter fetus	Endocarditis; mycotic aneurysm; lower-extremity thrombophlebitis or cellulitis in immunocompromised patients
DF-2	Dog bites; fulminant septicemia in asplenic persons
Clostridium septicum	Septicemia with distant myonecrosis; carcinoma of the colon
Lactobacillus species	Endocarditis with embolism in patients with underlying heart disease
Fusobacterium necrophorum	Occult abscess of the oral cavity or upper respiratory tract; suppurative thrombophlebitis of the internal jugular vein
Malassezia furfur	Seriously ill patients receiving hyperalimentation
Salmonella species, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Mycobacterium avium-M. intracellulare*	Persistent fever in patients with AIDS

[a] For fuller discussion and references, see text.

There is wide consensus that methicillin-resistant strains of *S. aureus* should be considered clinically resistant to all beta-lactam antibiotics, irrespective of susceptibility test results. The emergence of such strains in hospitals has complicated the design of presumptive drug therapy regimens for patients with suspected septicemia. In Detroit, Mich., the appearance of methicillin-resistant strains in the community was correlated with the widespread use of cephalexin among intravenous drug abusers in the city (288). It seems possible that the widespread appearance of such strains in hospitals during the 1980s may similarly have been due to heavy use of cephalosporin antibiotics.

Coagulase-negative staphylococci. The biologic diversity of the coagulase-negative staphylococci, long familiar to microbiologists, is now being appreciated by clinicians (202). However, determining which isolates are significant and which are contaminants remains problematic. Laboratory findings that suggest their role as true pathogens include the rapid isolation of bacteria from more than one culture, high intensity of bacteremia (CFU per milliliter), and the same biotypes and antibiotic susceptibility patterns of sequential isolates (150, 183). Antibiotic-resistant, slime-producing strains of *S. epidermidis* are given special credence (98). However, species other than *S. epidermidis* can also be significant. Occasionally, special studies such as phage typing and plasmid analysis of multiple isolates may be useful for building the case for pathogenicity (51). Laboratory personnel should consider saving coagulase-negative staphylococcal blood isolates for at least several weeks so that such comparisons can be made if indicated.

First identified as pathogens among patients with such foreign bodies as cerebrospinal fluid shunts and prosthetic heart valves, the coagulase-negative staphylococci continue to be a dreaded adversary of the implant surgeon. The ability of these bacteria to cause delayed infections after the placement of orthopedic devices or vascular grafts seems to be due, at least in part, to their ability to survive in a protective biofilm. The rising incidence of serious nosocomial septicemia related to vascular access lines is of major concern (269, 312). The crude mortality rate associated with true coagulase-negative staphylococcal bacteremia was recently determined to be 31 to 34% in two general hospital series (216, 258) and 46% among patients on a surgery service (63). The attributable mortality was determined to be 14% in one of these studies, but the median time from infection to death was 25 days (216). Patients receiving immunosuppressive therapy are also at high risk (361). Coagulase-negative staphylococci also appear to be significant nosocomial bloodstream pathogens in critically ill newborn infants (95, 290). Therapy of nosocomial coagulase-negative staphylococcal infection is made difficult by their widespread methicillin resistance.

***Streptococcus pneumoniae*.** Accurate diagnosis of pneumococcal pneumonia continues to be difficult despite improved criteria for the interpretation of sputum specimens (251). Documentation of bacteremia remains extremely helpful, despite the caveat that positive blood cultures are generally obtained only in the more severe cases. In 1964, Austrian and Gold reported that antibiotics had dramatically lowered the eventual mortality from bacteremia pneumococcal pneumoniae, yet had little impact on the death rate during the first several days of the illness (15). This observation still holds despite improvements in intensive care methods (160, 190). Although the mortality associated with bacteremic pneumococcal pneumonia was only 7% in one recent study (249), most investigators have found the mortality to be 20% or higher. Mortality is especially high among the elderly. Among younger patients, the association of alcoholism, leukopenia, and pneumococcal septicemia carries a poor prognosis (253). These findings confirm the need for liberal use of a pneumococcal vaccine among patients at high risk (297).

Identification of *S. pneumoniae* in blood cultures usually permits the clinician to simplify the patient's initial presump-

tive antimicrobial regimen. Blood isolates should be screened for possible relative resistance to penicillin G (321). Penicillin resistance is often associated with identifiable risk factors such as prior hospitalization, recent episodes of pneumonia, prior antibiotic therapy, and critical condition on arrival at the hospital (250). Laboratory personnel must now be alert also to the possibility of optochin-resistant pneumococci (187). Serotyping of blood isolates, at least in reference laboratories or major centers, is important to ascertain that the most prevalent serotypes are included in vaccine formulations (107, 371). Serious pneumococcal disease seems destined to continue to be a major worldwide problem, with important regional differences (64, 133).

The viridans streptococci. Although isolation of viridans streptococci from blood cultures may represent contamination in up to one-half of instances, the association with endocarditis remains strong. Although the percentage of all endocarditis cases that are due to this heterogeneous group of bacteria has declined over the years, they still account for the majority of cases in most series. *S. mitior* and *S. sanguis* are the most frequent species associated with this complication (276).

It is essential that laboratories be capable of isolating vitamin B6-dependent strains. During two separate periods at New York Hospital between 1944 and 1978, such strains accounted for 5 to 6% of endocarditis cases (277). Hence, media should be supplemented with one of the active forms of vitamin B6: pyridoxal hydrochloride or pyridoxamine dihydrochloride. Concern has been expressed that these pyridoxal-dependent strains may not be adequately detected by the lysis-centrifugation blood culture system (311). This observation underscores the importance of using more than one blood culture system in suspected but difficult-to-confirm cases of endocarditis. It is helpful for the laboratory to determine whether the isolate is exquisitely susceptible to penicillin G (usually defined by a minimum inhibitory concentration of no greater than 0.1 μg/ml), since more resistant isolates may require longer therapy.

The extent to which the viridans streptococci cause syndromes other than endocarditis remains somewhat controversial. It has been suggested that isolation of these bacteria from blood cultures obtained from cancer patients with pulmonary infiltrates may explain the etiology of pneumonia (229). There has been considerable interest in the pathogenicity of *S. anginosus* (previously known by a variety of names including "*Streptococcus* MG" and "*S. milleri*"). This species has been frequently associated with suppurative infections, most notably, brain abscesses (293). Although one recent reviewer concludes that the evidence that "*S. milleri*" is uniquely associated with suppurative infections is "scattered and mainly circumstantial" (131), most published studies support this contention (282). The clinical value of routine species identification of viridans streptococci is not firmly established.

Group A streptococci (*S. pyogenes*). Prior to the introduction of penicillin, *S. pyogenes* exacted terrible mortality rates, especially among the battlefield wounded and postpartum women (70). Advanced age and serious underlying disease were recognized as adverse prognostic factors (177). In 1937, Keefer et al. reported the crude mortality of group A streptococcal bacteremia to be 90% when secondary to operative wounds, 83% when secondary to pneumonia, 80% when secondary to cellulitis or erysipelas, 56% when secondary to pelvic infection, and 55% when secondary to upper respiratory infection, otitis media, or mastoiditis (177). The introduction of antibiotics lowered not only the mortality but also the incidence of this bacteremia. Today, death from puerperal sepsis is distinctly uncommon (60). Since the advent of penicillin, concern about group A streptococci has centered mainly around mucocutaneous disease (pharyngitis, impetigo) and nonsuppurative sequelae (rheumatic fever, acute glomerulonephritis).

Nevertheless, fulminant group A streptococcal bacteremia still occurs. In a recent series of predominantly community-acquired cases, mortality was 35% overall and 60% among patients who experienced shock (165). In both children and adults, group A streptococcal bacteremia often points to skin infection and underlying disease (29, 365). Most recent reports in adults have emphasized compromised host defenses. These include tumors, diabetes mellitus, alcoholism, connective tissue diseases, or the use of immunosuppressive drugs or irradiation therapy. An outbreak among intravenous drug abusers was noteworthy for the prominence of gastrointestinal symptoms and for the possibility of person-to-person transmission related to a common source (19). Among the elderly, this bacteremia can not only be fulminant, but can also mimic a primary vasculitis and thus be difficult to recognize (130).

Group B streptococci (*S. agalactiae*). The syndromes of group B streptococcal bacteremia among newborn infants and postpartum women are now widely appreciated. It is now also well appreciated that group B streptococci can behave as opportunistic nosocomial pathogens, especially among patients with malignancy, alcoholism, chronic renal failure, cirrhosis, diabetes mellitus, and peripheral vascular disease (196). The combination of diabetes and peripheral vascular disease is frequent. In one recent study, the crude mortality associated with group B streptococcal bacteremia was 15% among infants but 38% among adults (248). However, the extent of attributable mortality is often unclear since many such cases are polymicrobial, low grade, or of short duration, with death being largely due to underlying diseases (335). Therapeutically, concern continues to be expressed that incremental increases in the minimum inhibitory concentrations of penicillin G against this microorganism may require the addition of an aminoglycoside antibiotic for synergism.

Enterococci. The enterococci (notably *E. faecalis*, *E. faecium*, and *E. durans*) now account for 10 to 20% of all cases of endocarditis. Heavy use of cephalosporin antibiotics, to which enterococci are characteristically resistant, explains at least in part the increased recognition of nosocomial enterococcal bacteremia (370). *E. faecium* is one of the few microorganisms resistant to the carbapenem antibiotic imipenem, which also might be expected to select out enterococci. Enterococcal bacteremia characteristically arises from the patient's normal flora and is often part of a polymicrobial septicemia. However, it can also appear in epidemic form in the intensive care unit setting (203).

Maki and Agger found associated endocarditis in 12 of 35 community-acquired enterococcal bacteremias but in only 1 of 118 nosocomial enterococcal bacteremias (207). Isolation of enterococci from blood cultures in cases in which endocarditis seems unlikely confronts the clinician with a therapeutic dilemma. Optimum therapy of enterococcal infection requires two antibiotics: generally, high-dose penicillin G, ampicillin, or vancomycin plus an aminoglycoside. Strains highly resistant to the aminoglycosides are becoming increasingly common, and even vancomycin-resistant enterococci have been described (174). The literature contains conflicting data with regard to the extent that enterococci are a cause of death. In one study, crude mortality was 39% but

attributable mortality was only 7% (56); in another, crude mortality was 30% and attributable mortality was 12% (141). In one study, only 20% of deaths occurred within 72 h of the first positive blood cultures (56); in another, 43% of deaths occurred within this time frame (271). Recent studies suggest that appropriate therapy directed against enterococci improves the outcome for many patients (207, 271). Still, a significant minority recover without antimicrobial therapy, and thus therapeutic decisions must be individualized (141).

Streptococcus bovis. Recognition in blood cultures of nonenterococcal group D streptococci (for practical purposes, synonymous with *S. bovis*) carries two implications. First, appropriate therapy resembles that given for the viridans group of streptococci rather than that required by the more difficult to treat enterococci. Second, gastrointestinal neoplasia must be excluded. Klein et al. reported in 1977 the now well-known association of *S. bovis* bacteremia with carcinoma or villous adenoma of the colon (184). These authors also recognized that patients with carcinoma of the colon were more likely to harbor *S. bovis* in their stools. Rarely, *S. bovis* bacteremia is associated with carcinoma of the stomach as well, indicating the need for a complete evaluation of the gastrointestinal tract (119). More recently, it was determined by analysis of tumor registries that 17% of 90 patients who had experienced *S. bovis* bacteremia between 1951 and 1980 had developed carcinoma of the colon by 1987 (Honberg and Gutschik, Letter, Lancet **i**:163–164, 1987). Therefore, isolation of *S. bovis* from blood cultures indicates that close scrutiny of the gastrointestinal tract must be long term, not short term.

Non-group A, B, or D streptococci. Recognition of serious infections due to streptococci belonging to Lancefield groups other than groups A, B, and D has increased in recent years. Among these, group C and, especially, group G tend to predominate (299). Malignancy is present in one- to two-thirds of patients with group G streptococcal bacteremia. Alcoholism and diabetes mellitus are also common associations. The infection can present as a primary bacteremia, as well as a localized infection such as pneumonia, cellulitis, or osteomyelitis (14, 330). In one series, 47% of patients with group G streptococcal bacteremia had acute endocarditis (332). However, in another experience the attributable mortality was only 8%, suggesting that group G streptococcal bacteremia can be a relatively benign illness (299). It has been suggested that Lancefield typing of all beta-hemolytic streptococci, made feasible by rapid and widely available methods, should be carried out routinely.

***Corynebacterium* species.** The nondiphtheria corynebacteria are a diverse group of microorganisms that can be contaminants but which can also be associated with a wide variety of syndromes (199). Pathogenicity of these microorganisms has been established, especially in patients with neurosurgical shunts or prosthetic heart valves.

In 1976, Hande et al. described four patients with a unique *Corynebacterium* species in blood, characterized by a metallic sheen on blood agar plates and by resistance to most antibiotics, including penicillin, but susceptible to vancomycin. All of the patients had underlying illness, usually leukemia (144). Now referred to as "*Corynebacterium* JK," "CDC-JK," or "JK diphtheroids," these microorganisms have emerged as important pathogens at major oncology centers (144, 268, 291). Characteristically, affected patients have had extended granulocytopenia related to therapy for hematologic neoplasms or have received broad-spectrum antibiotics or both. These bacteremias typically arise from a defect in the skin or mucous membranes, and most are secondary to vascular access devices (291). It should be emphasized that, as with other nondiphtheria corynebacteria, the majority of *Corynebacterium* JK isolates are contaminants. However, as many as 20% of *Corynebacterium* JK blood isolates are indicative of serious nosocomial infections (268). The repeated isolation of diphtheroid organisms from blood, cerebrospinal fluid, or other normally sterile body fluids strongly suggests such infection. Meticulous hygiene has been shown to be protective against this bacteremia, and such prevention is important not only because of the consequences of the bacteremia but also because of the requirement for vancomycin therapy.

Listeria monocytogenes. Listeriosis causes approximately 150 deaths in the United States each year, attack rates being highest in neonates and the elderly. Between these extremes of life, nonpregnant persons with *Listeria* bacteremia should be suspected of having underlying diseases, especially neoplasms. *L. monocytogenes* is an intracellular pathogen, and thus impairment of T-lymphocyte function predisposes to this infection (72). Meningitis is the best-known syndrome of life-threatening *Listeria* infection, but endocarditis also occurs. Approximately 40% of patients with *Listeria* endocarditis do not have underlying heart disease but develop this complication when *Listeria* bacteremia occurs during the course of an underlying event such as neoplasm, lymphoma, septic abortion, or immunosuppressive therapy. *Listeria* endocarditis results in septic complications in up to 50% of cases (66). The incidence of serious *Listeria* infection may be underestimated due in part to the readiness with which the organism can be misidentified as either a diphtheroid contaminant or a *Streptococcus* species. An increased frequency of *Listeria* isolates within a geographic area raises the possibility of an epidemic related to dairy products (198).

***Bacillus* species infections.** Isolates other than *B. anthracis* (the cause of anthrax) are usually regarded as contaminants, but it has been recognized for some time that these organisms can be true pathogens, especially in cancer patients. As is the case with the coagulase-negative staphylococci, multiple positive blood cultures help establish the case for pathogenicity. Most commonly, *Bacillus* species bacteremia has been related to vascular access catheters or intravenous drug abuse (300). Although *Bacillus* species bacteremia has been regarded, in most cases, as "not a particularly serious disease" (300), experience indicates that failure to remove implicated catheters is associated with a high rate of recurrence (17, 80). One species, *B. cereus*, has been called a "snake in the grass" capable of causing a fulminant illness in granulocytopenic patients with hematologic neoplasms (H. F. L. Guiot, M. M. dePlanque, D. J. Richel, and J. W. van't Wout, Letter, J. Infect. Dis. **153**:1186, 1986). The resistance of *B. cereus* to most beta-lactam antibiotics makes vancomycin the drug of choice for *Bacillus* infection, at least until species identification and susceptibility testing have been carried out (341).

Erysipelothrix rhusiopathiae. Classically, *Erysipelothrix rhusiopathiae* causes a self-limited cellulitis after a skin wound obtained from handling infected animals, food, or water ("fish handlers' disease"). Blood isolates usually indicate a uniquely occupational endocarditis. Of the 49 reported cases of serious *E. rhusiopathiae* disease, 90% have been either strongly suspected or proven cases of endocarditis. This form of endocarditis affects primarily men, usually involves the aortic valve, and has a high correlation with occupations involving animal exposure. *E. rhusiopathiae* is typically penicillin susceptible but resistant to vancomycin. Since vancomycin is often used for presumptive therapy of

endocarditis, laboratories must distinguish this gram-positive rod from others to avoid delays in the institution of effective antibiotic therapy (129). *E. rhusiopathiae* is also capable of causing fulminant bacteremia with septic shock (247).

Aerobic Gram-Negative Bacteria

***Neisseria* species.** *N. meningitidis* is one of the few microorganisms capable of killing a previously healthy person within a few hours. Although most cases now represent sporadic rather than epidemic disease, prompt reporting to health authorities remains mandatory (136). Isolation of *N. gonorrhoeae* from blood cultures is more likely to indicate the tenosynovitis-dermatitis syndrome than suppurative arthritis with joint effusions. These isolates are usually resistant to the normal bactericidal activity of human serum (246) but are nearly always susceptible to penicillin G. The association of recurrent neisserial bacteremia with late-acting complement deficiencies has already been mentioned.

The nongonococcal, nonmeningococcal neisseria are infrequently isolated from blood cultures but can be pathogenic. In one recent study, it was determined that four of eight such isolates were associated with life-threatening disease: endocarditis (two instances), septicemia, and meningitis. The others were contaminants (109). *Neisseria mucosus* (*Neisseria mucosa*), a part of the normal mouth flora, was recently associated with bacteremia, the adult respiratory distress syndrome, and death in a patient who had experienced a near-drowning episode (211).

***Haemophilus influenzae*.** *H. influenzae* type b continues to be a scourge of childhood between the waning of maternal antibodies by 3 months and the appearance of one's own antibodies by age 6. Although the mortality from *H. influenzae* meningitis has been reduced to about 5%, the neurologic sequelae are still of major concern. Other childhood syndromes include cellulitis, epiglottitis, and septic arthritis. Children with high-intensity (>100 CFU/ml) bacteremia are more likely to have meningitis, whereas those with low-intensity (<100 CFU/ml) bacteremia are more likely to have cellulitis or arthritis (214). Children who do not seem to be seriously ill, that is, who present with occult or walk-in *H. influenzae* bacteremia, are nevertheless at risk of progression to serious disease (8).

Recognition of serious *H. influenzae* disease in adults has increased (156). Concern has been expressed that antibiotic therapy of childhood infections may blunt the development of bactericidal antibodies, so that many of today's adults lack acquired immunity to this pathogen. Among the syndromes are meningitis, epiglottitis, sinusitis, pneumonia, pericarditis, septic arthritis, cellulitis, pelvic infections, and overwhelming septicemia among asplenic persons. As is the case in children, most of these serious infections are due to type b strains. Nontypeable *H. influenzae* strains are being recognized with increased frequency as causes of septicemia among premature infants (120) and of lower respiratory tract infection among adults (238). Nationwide, type b strains are more likely (32 versus 16%) to demonstrate beta-lactamase-mediated resistance to ampicillin compared with nontypeable strains (94).

Other *Haemophilus* species. Bacteremia due to *H. parainfluenzae*, *H. aphrophilus*, and *H. paraphrophilus* often indicates endocarditis. Isolation of these slow-growing capnophilic species may require prolonged incubation or subculture or both but is especially important because of the associated high frequency of embolism to major arteries (71, 103). In one series, this occurred in six of seven young to middle-aged patients with *H. parainfluenzae* endocarditis (71). As a corollary, clots removed at the time of surgery (i.e., at embolectomy) should be cultured appropriately for these fastidious microorganisms. In the absence of endocarditis, these species and, notably, *H. aphrophilus* appear to be especially associated with trauma and cancer (30).

The family *Enterobacteriaceae*. No attempt will be made here to survey the voluminous literature on gram-negative septicemia, which often seems synonymous with bacteremia due to members of the family *Enterobacteriaceae*. In major series of bacteremias from teaching hospitals, the usual rank order of frequency of members of the *Enterobacteriaceae* is *E. coli* > *Klebsiella* spp. > *Serratia* spp. > *Enterobacter* spp. = *Proteus* spp. > others (367). Mortality remains high, especially among persons with severe underlying diseases and among the elderly (219). Mortality tends to be highest among patients with *Klebsiella* bacteremia and lowest among those with *E. coli* bacteremia (55). The literature bearing on individual members of the *Enterobacteriaceae* will be summarized briefly.

E. coli is the most common cause of enterobacterial bacteremia, especially because of its close association with bacteremic urinary tract infection (274). This may explain, in part, why *E. coli* carries the lowest attributable (bacteremia-related) mortality among the *Enterobacteriaceae* members, since urinary tract infection is associated with a lower mortality compared with most other sources of secondary bacteremia (53, 54). Recent studies focus especially on virulence factors such as P fimbriae. Blood isolates of *E. coli* from patients with anatomically normal urinary tracts nearly always have P fimbriae. This is not the case among patients with urinary tract abnormalities or otherwise compromised host defenses, presumably because added virulence factors are not necessary for *E. coli* to establish its foothold under these circumstances (171).

Klebsiella pneumoniae bacteremia may signify community-acquired pneumonia, but more often it is a nosocomial disease with a strong association with septic shock (122). *K. pneumoniae* often replaces *E. coli* as the predominant aerobic gram-negative rod in the gastrointestinal tracts of seriously ill hospitalized patients. Thus established, it can emerge from this reservoir to cause life-threatening infection. *Enterobacter* bacteremia is usually nosocomial and carries a 35 to 42% crude mortality rate (38, 62). It seems likely that the frequency of *Enterobacter* bacteremia will increase due to the continued heavy use of cephalosporin antibiotics in today's medical practice. *Enterobacter cloacae* is especially likely to develop plasmid-mediated drug resistance (49, 169).

Serratia bacteremia is hospital acquired in nearly all instances (37) and tends to be associated with especially long durations of hospitalization. Like *Enterobacter* spp., *Serratia* species are often antibiotic resistant. The urinary tracts of older catheterized patients provide a reservoir for such drug-resistant strains, which may then be spread throughout a hospital or even from one hospital to another throughout a metropolitan area (289).

Proteus bacteremia is especially associated with urinary tract infections in younger patients and more serious nosocomial infections among hospitalized patients, especially the elderly (2, 231). *Providencia* bacteremia, uncommon in most series, has been associated especially with urologic disease and paraplegia (179). Some strains of *Providencia stuartii* seem to be especially able to invade the urinary tract (170), perhaps explaining why it was recently found to be the most

frequent gram-negative blood isolate at a Veterans Administration extended care facility (281). *Citrobacter diversus* bacteremia is also frequently of urinary tract origin. However, *Citrobacter* bacteremia, and especially *C. freundii* bacteremia, should also suggest disease of the gallbladder or small bowel (96, 197). *Morganella morganii* bacteremia most often arises from postoperative wound infections in patients who have received broad-spectrum antibiotics (220). It may especially be associated with cardiovascular surgery (357). *Edwardsiella tarda* bacteremia is often associated with septic shock and carries a 50% crude mortality, possibly because of its usual association with underlying illness (358). No attempt will be made here to summarize the experience with newer members of the *Enterobacteriaceae*, many of which are still of unclear clinical significance (118).

***Salmonella* and *Shigella* species.** It is customary to treat *Salmonella* and *Shigella* species separately from the other members of the *Enterobacteriaceae* because of their unique associations with gastrointestinal disease. The transient bacteremia that occurs during the course of uncomplicated *Salmonella* bacteremia can cause disease in previously damaged tissues, including atherosclerotic plaques. The risk of life-threatening mycotic aneurysms, especially of the aorta, increases after age 50 (73). *Salmonella cholerae-suis* was formerly the most frequent species associated with this complication but is being replaced especially by *Salmonella enteritidis* and *Salmonella typhimurium* (252).

Localized *Salmonella* infection and enteric fever give rise to intermittent or sustained bacteremia, made worse by any underlying impairment of T-lymphocyte or macrophage function. Diseases that cause macrophage "blockade" notoriously predispose to *Salmonella* infection. Disseminated histoplasmosis was recently added to the classic examples: sickle cell anemia, malaria, bartonellosis, and louse-borne relapsing fever (350). The well-known association between *Salmonella* bacteremia and malignancy reflects, at least in part, impairment of T-lymphocyte function. AIDS not only predisposes its victims to *Salmonella* bacteremia, but also compromises their abilities to rid these bacteria from the bloodstream (112, 308)

Shigella bacteremia has been considered uncommon, occurring mainly among children with underlying problems such as malnutrition, neoplasms, or hemoglobinopathies (234, 318). Recently, *Shigella* bacteremia has been especially noted among elderly patients and immunocompromised patients, in whom it is associated with a high mortality (234). *Shigella* bacteremia is also emerging as an important problem among patients infected with the human immunodeficiency virus, although it has yet to be recognized as an AIDS-defining condition (21).

The family *Pseudomonadaceae*. Nearly all investigators of gram-negative septicemia have found the highest mortality rates to occur among patients infected by *Pseudomonas aeruginosa* (55, 367). This bacteremia is nearly always nosocomial and typically occurs among patients with severe underlying disease. After establishing its foothold, *P. aeruginosa* unleashes not only a biologically active endotoxin, but also other virulence factors such as exotoxin A. The relative frequency of *P. aeruginosa* bacteremia appears to be increasing, although the experience varies considerably among different medical centers (85). In one recent study, crude mortality was 50%, and it was concluded that efforts should be placed primarily on prevention and on the development of new treatment modalities (31). However, Bodey et al. reported a 37% mortality among patients with cancer, the majority of whom had acute leukemia. Survival correlated with effective antibiotic therapy, and a 1- to 2-day delay prior to giving the proper agents reduced the cure rate from 74 to 46% (34). Hence, prompt recognition of *P. aeruginosa* in blood cultures is extremely important.

Pseudomonadaceae members other than *P. aeruginosa* occasionally cause community-acquired infections such as endocarditis in intravenous drug abusers. However, they are best known as opportunistic nosocomial pathogens capable of causing point-source epidemics. *P. maltophilia* is currently the most common blood isolate among these pseudomonads and causes a wide spectrum of disease. The attributable mortality is relatively low despite its resistance to many antibiotics (372). *P. cepacia* has caused a large number of outbreaks, nearly all of which have been traced to its remarkable ability to multiply in water or in moist environments. Recent examples of such outbreaks were associated with a blood gas analyzer (152) and with the water reservoir of an intra-aortic balloon pump (284). *P. maltophilia* and *P. cepacia* belong to the small group of microorganisms characteristically resistant to imipenem; hence, they might be expected to emerge as important pathogens, especially at hospitals where this new, unusually broad-spectrum antibiotic is heavily used. An indolent bacteremia due to *P. putrefaciens* is characteristically secondary to infection of the lower extremity; this organism can also cause fulminant septicemia associated with cancer, cirrhosis, or other severe underlying disease (181).

***Acinetobacter calcoaceticus*.** Disease due to *Acinetobacter* species is nearly always nosocomial and occurs especially during the summer months. Bacteremias are most frequently primary infections (272). Typical risk factors include vascular access lines, hemodynamic monitoring equipment, and prior antibiotic therapy. Shock is common and associated mortality is high (126). Recently, an association of *Acinetobacter* bacteremia with malignancies has been emphasized in both adults (278) and children (121). Recognition of *Acinetobacter* species is important because appropriate therapy more nearly resembles that used for *Pseudomonas aeruginosa* infection than regimens recommended for infections due to the common *Enterobacteriaceae* members.

***Aeromonas hydrophila*.** *Aeromonas* is best known for severe soft-tissue infections arising in wounds exposed to fresh water, its usual habitat. Bacteremia occurs especially among patients with cirrhosis or malignancies (89, 195). In a review of the literature through 1977, crude mortality was determined to be 61% among patients with cirrhosis or malignancy and 50% among patients without these associations. Among patients with malignancies who have experienced *Aeromonas* bacteremia, some investigators (362), but not others (147), report a characteristic history of exposure to fresh or salt water or to fish. Alternatively, the organism might arise from tap water or from the patient's own gastrointestinal tract.

***Pasteurella multocida*.** Bacteremia is a somewhat unusual complication of *P. multocida* infection, which commonly causes wound infections, including osteomyelitis, following bites or scratches from animals, especially cats (342). Again, there is a strong association with malignancy and especially with cirrhosis (260). Localized infection is common in these patients, up to 30% of whom may lack the characteristic history of animal exposure.

***Yersinia* species.** It was recently reported from New Mexico that septicemia was present among 25% of patients with plague (*Yersinia pestis*). The risk of septicemia was greatest among older patients, but deaths were especially common among patients <30 years of age. The signs and symptoms

resembled those of other causes of septicemia, with abdominal pain being present in nearly one-half of the patients. It was suggested that deaths from septicemic plague could be reduced by aggressive antimicrobial therapy or suspected gram-negative septicemia. Aminoglycoside antibiotics remain the drugs of choice (163).

Y. enterocolitica and *Y. pseudotuberculosis* usually cause enteric disease, most commonly ileitis or mesenteric lymphadenitis. Septicemia is uncommon, but is likely to occur especially among patients with liver disease or iron overload. Occasionally, *Y. pseudotuberculosis* septicemia can present as multiple liver abscesses (108).

***Vibrio* species.** The increased frequency with which disease due to the noncholera vibrios is recognized is of wide current interest. Ingestion of shellfish (notably, raw oysters) is a common exposure history, and liver disease markedly predisposes to septicemia. The non-O-1 *Vibrio cholerae* organisms usually cause diarrheal disease but occasionally cause septicemia, especially among patients with cirrhosis or hematologic malignancy. In a recent review of the literature, the crude mortality was determined to be 62% (286).

A more frequent problem in the United States is septicemia due to *V. vulnificus*. Characteristically, patients are men aged 40 years or older with underlying liver disease who have recently ingested raw oysters (322). Endocarditis occurs rarely (325), but skin lesions are common. These range from wound infections (as a primary portal of entry) to secondary lesions such as hemorrhagic bullae, cellulitis, necrotizing fasciitis, and gangrene (157). The high associated mortality suggests the need for aggressive therapy (185). Bacteremias due to a variety of other *Vibrio* species, including newly described ones, continue to be reported (40, 261).

***Campylobacter* species.** *Campylobacter fetus*, compared with *Campylobacter jejuni*, is less often associated with an acute enteritis syndrome but is more likely to cause bacteremia. *C. fetus* bacteremia can lead to a variety of localized infections, including meningitis. Most characteristic, however, are endovascular infections such as endocarditis, mycotic aneurysm, and thrombophlebitis. Lower-extremity thrombophlebitis or cellulitis seems to be a frequent presentation among the immunocompromised (115). Among healthy persons, *C. fetus* bacteremia may be a transient event in the course of self-limited diarrheal illness (138).

C. jejuni is commonly isolated from stools but infrequently from blood cultures. Approximately one-half of the reported cases of bacteremia have been associated with severe underlying disease, and most of the remaining cases have occurred among either infants or the elderly (91). Whether *Campylobacter* species are underrecognized in blood cultures is unclear. In one recent report, *Campylobacter* sp. was isolated from blood cultures only after the introduction of the radiometric method (305). It was also noted that it may take longer than 7 days to isolate *Campylobacter* spp. from blood cultures. Hence, a history of recent diarrhea or a positive stool culture should prompt the holding of blood cultures for a longer duration than might be customary.

Dysgonic fermenters. Bacteremia due to *Capnocytophaga* species, formerly dysgonic fermenter 1 (DF-1), tends to occur among children who have granulocytopenia and mucosal deficits (337). DF-2, a newly described pathogen, is a slow-growing gram-negative bacillus causing a zoonotic infection acquired from dogs. Among patients with bacteremia, 80% have had a history of dog bite or dog exposure. Asplenic patients are likely to develop fulminant septicemia with disseminated intravascular coagulation and peripheral gangrene. Persons suffering from alcoholism or cirrhosis or both seem to constitute the other major risk group but have a milder illness. The overall mortality has been 27% (154). Apparently, DF-2 can cause a false-positive latex agglutination test for cryptococcal antigen in the cerebrospinal fluid. This point is important because these patients can have headache as part of their illnesses and thus the latex test may be ordered (349). DF-2 is susceptible to nearly all antibiotics including penicillin (334). Bacteremia due to a still-newer species, DF-3, was recently reported in a granulocytopenic patient with acute leukemia (13).

Other gram-negative bacteria. Bacteremias due to some of the other species of gram-negative bacteria will be mentioned in passing. *Cardiobacterium hominis* and *Actinobacillus actinomycetemcomitans* are fastidious slow-growing organisms sometimes associated with endocarditis on either native or prosthetic valves. Major systemic emboli and heart failure occur in about one-half of these cases of endocarditis (132, 175, 364). Brucellosis, which is probably underdiagnosed in the United States at present, should also be remembered as a cause of culture-negative endocarditis often requiring surgery for cure (366). In a large recent series from Kuwait, 14% of patients with brucellosis had positive blood cultures (237). Isolation of *Francisella tularensis* from blood cultures in cases of tularemia has been reported mainly in patients with underlying diseases, but the clinical significance of these positive blood cultures is unclear (S. A. Klotz, R. L. Penn, and J. M. Provenza, Editorial, Arch. Intern. Med. **147**:214, 1987). *Legionella pneumophila* has been isolated from blood, especially from immunocompromised patients (T. F. Marrie and R. S. Martin, J. Infect. Letter, **16**:203–204, 1988). Newer blood culture systems hold the promise of more rapid diagnosis of *Legionella* bacteremia (264, 270).

Achromobacter xylosoxidans is a rare cause of bacteremia in older patients, is typically hospital acquired, and is associated with a high mortality (210). Bacteremia due to *Eikenella corrodens*, part of the normal flora, has been associated with internal jugular vein thrombophlebitis in previously healthy persons (68) and overwhelming infections among the immunocompromised (320). *Flavobacterium meningosepticum* and *Flavobacterium* species group IIb are potential contaminants of the hospital as well as of the natural environment and are important to recognize, especially because of their characteristic resistances to many antibiotics (158, 296). *Chromobacterium violaceum* is another gram-negative rod found naturally in soil and water; the occasional bacteremias have usually been fatal (33, 356). *Kingella kingae* bacteremia has been associated with endocarditis or bone and joint infections in children (145) and rarely causes bacteremia in granulocytopenic cancer patients (178). Occasional reports document bacteremias due to infrequently encountered gram-negative microorganisms, especially among the immunocompromised. Recent examples include *Sphingobacterium multivorum* (117) and CDC (Centers for Disease Control) group IV c-2 (86).

Anaerobic Bacteria

By the 1970s, improved culture methods resulted in increased recognition of bloodstream infections due to anaerobic bacteria. In recent years, the incidence of anaerobic bacteremias has stabilized or even decreased at some medical centers. In one large recent series of anaerobic bacteremia, 46% of isolates were gram-negative bacilli (especially *Bacteroides fragilis*) and 38% were gram-positive bacilli (especially *Clostridium perfringens*). Polymicrobial bactere-

mia was common, septic shock occurred in about one-fourth of patients, and surgery was often essential (331). These findings illustrate the seriousness of anaerobic bacteremia. Isolation of anaerobic bacteria from blood cultures frequently signifies a major disruption of epithelium. This is the case because, compared with aerobic pathogens, the ability of anaerobic bacteria to cross intact or minimally damaged epithelial barriers and thereby gain access to the bloodstream is limited (310). Even among granulocytopenic patients with cancer, anaerobic bacteremia seldom occurs in the absence of obvious disruption of epithelium (44).

Proper interpretation of the significance of anaerobic blood isolates, especially anaerobic gram-positive bacilli, often requires close clinical correlation. In a 1972 report, it was determined that only 1.8% of patients from whom anaerobic, nonsporeforming, gram-positive bacilli were isolated from blood and only 50% of patients from whom sporeforming bacilli were isolated had clinical pictures consistent with septicemia (359). In recent reports the crude mortality associated with clostridial bacteremia has been 45 to 48% (164, 243); however, the extent of attributable mortality is unclear. These bacteremias are often polymicrobial and tend to occur among severely debilitated patients (243). In mixed intra-abdominal infection, it is unclear whether therapy directed specifically against clostridia improves survival (168). The clinical significance of *Clostridium perfringens* blood isolates requires careful judgment because of the classic association of this microorganism with overwhelming toxicity, including massive intravascular hemolysis.

The association of *Clostridium septicum* bacteremia with malignancy is now well known (188). It was determined recently that 81% of the reported cases of *Clostridium septicum* infection have been associated with malignancy; 40% of the patients had hematologic malignancy and 34% had carcinoma of the colon (189). The specific association of *Clostridium septicum* bacteremia with carcinoma of the colon, including occult carcinoma, resembles that of *Streptococcus bovis*. Patients with *Clostridium septicum* bloodstream infection can present with gangrene distant from the site of infection (distant myonecrosis), and prompt antimicrobial therapy seems to be imperative (189). *Clostridium tertium* septicemia has now been correlated with hematologic malignancy and neutropenia (304). The crude mortality among patients with leukemia and clostridial bacteremia was 78% in a recent series in which *Clostridium septicum* was the most common isolate. No patient with intravascular hemolysis survived (67). Prompt recognition of clostridial bacteremia is important, especially because clostridia may be resistant to certain antibiotics now commonly used for presumptive therapy, such as the cephalosporins.

Lactobacillus species bacteremia can be a complication of late pregnancy and the postpartum period and can also occur in newborn infants (81). Among patients with underlying heart disease, *Lactobacillus* species bacteremia may signify the presence of endocarditis, with a high likelihood of embolism (319).

The strong association of *Bacteroides fragilis* bacteremia with mixed intra-abdominal and pelvic infections requires little comment. Both surgery and appropriate antimicrobial therapy are frequently necessary (245). In one study, the crude and attributable mortality rates associated with *Bacteroides* bacteremia were 41 and 18%, respectively (58). Encapsulation, previously found to be an important virulence factor for abscess formation by *Bacteroides fragilis*, may also be important for bloodstream invasion (43). The changing susceptibilities of *Bacteroides fragilis* to antimicrobial agents continues to be of great concern, and it has been suggested that each institution should monitor its own experience (87).

Some other recent clinically pertinent observations include the recognition that *Fusobacterium necrophorum* possesses a biologically active endotoxin, that the resistance of *Bacteroides melaninogenicus* to penicillin is increasing, and that newer antibiotics may eliminate the need for surgical drainage of abscesses in carefully selected patients (20). Unexplained *Fusobacterium* species bacteremia raises the possibility of an occult abscess of the upper respiratory tract and oral cavity (153). *Fusobacterium* species, and especially *Fusobacterium necrophorum*, are strikingly associated with suppurative thrombophlebitis of the internal jugular vein. Recognition of this life-threatening complication, known as the Lemierre syndrome, enables successful therapy in most instances (298). Bacteremia due to peptococci and peptostreptococci most often occurs among postpartum women (324). Bacteremia due to *Anaerobiospirillum succiniciproducens*, an unusual spiral anaerobic bacterium first isolated from beagles, is usually preceded by gastrointestinal tract signs and symptoms suggesting prior colonization (227). The potential for these and other anaerobic bacteria to cause somewhat unique syndromes underscores the prominence of anaerobic bacteria among the normal microbial flora.

Fungi

The rising incidence of nosocomial fungemia, especially due to *Candida* species, may be attributable in part to more sensitive blood culture systems (139, 344). However, there can be little doubt that it also reflects changing patterns of medical care. These infections typically occur in critically ill patients with risk factors such as hyperalimentation, hemodynamic monitoring devices, and previous broad-spectrum antimicrobial therapy. Underlying tumors are also common (161). Although crude mortality has been 45 to 79% in recently published series (102, 149), the attributable mortality is unclear. On the one hand, therapy with amphotericin B definitely improves survival, at least among postoperative surgical patients (302). On the other hand, it is suggested that fungemia due to *Candida* species sometimes indicates collapse of host defenses and hence a poor prognosis irrespective of therapy (100).

With regard to the latter notion, it has been suggested that *Candida* species gain access to the bloodstream through small ulcerations in the gastrointestinal mucosa. These occur among patients who in previous years would have already succumbed from their underlying diseases. Hence, such episodes of fungemia might "be viewed more appropriately as a consequence of the support technology of the 1980s" (100). Confronted with a *Candida* blood isolate in a patient at risk to progressive multiple organ failure, the physician must choose whether to add the risk of amphotericin B nephrotoxicity. The recent recognition of amphotericin B-resistant yeast strains among blood culture isolates only heightens the clinician's dilemma (259).

Although the importance of aspergillosis and mucormycosis especially as opportunistic infections among immunosuppressed patients is well known, positive blood cultures are uncommon. In none of 29 reported cases of *Aspergillus* species endocarditis unrelated to prior heart surgery were blood cultures confirmatory (363).

Recently, *Fusarium* species have been recognized as major pathogens among cancer patients, with positive blood

cultures not being unusual (7). Blood cultures were positive in three of four patients with disseminated disease. All patients with deep-seated disease remained neutropenic and died (7). Patients with disseminated fusarial infection often have multiple skin lesions and orbitofacial involvement (267). *Malassezia furfur*, previously known only as the cause of a benign skin condition (tinea versicolor), has caused fungemia among seriously ill neonates and adults who were receiving hyperalimentation. Apparently, the intravenous fat emulsions used for hyperalimentation support the growth of this lipophilic yeast. Symptoms resolve upon removal of the colonized central venous catheter (88). *Hansenula anomala* is another example of an emerging fungal pathogen capable of causing a wide spectrum of disease among immunocompromised patients (146).

Cryptococcus neoformans is the most common fungus isolated from blood cultures of patients with AIDS (105), another setting in which the problem of fungemia is rising dramatically. In both endemic and nonendemic zones, *Histoplasma capsulatum* can also be isolated from the blood of AIDS patients and may represent either the acute overwhelming or the progressive disseminated form of this infection (172). In a recent analysis of fungemia due to *Coccidiodes immitis*, it was determined that 11 of 16 patients, most of whom had compromising underlying conditions, died within 1 month (6). Although certain fungal organisms found in blood cultures may be of low virulence (28), the rising problem of fungemia requires development of new therapeutic modalities and, even more important, new strategies for prevention.

Mycobacteria

Transient mycobacteremia due to *Mycobacterium tuberculosis* occurs during the primary infection and is often asymptomatic. Newer blood culture systems, specifically, the lysis-centrifugation method, may lead to more frequent documentation of *M. tuberculosis* in blood cultures among symptomatic patients (180). More recently, isolation of the *M. avium-intracellulare* complex (or *M. avium*) has assumed clinical importance in the management of AIDS. Persistent fever with a negative diagnostic evaluation for other pathogens is an important clue to disseminated *M. avium* disease in these patients (257). Both lysis-centrifugation and radiometric systems have been found to be helpful (368). Disseminated *M. avium* disease can also occur in patients without AIDS and can sometimes be treated successfully (162). It should be sought especially among patients with hairy cell leukemia (25). However, therapy for this condition commonly calls for the use of five or six drugs (76); advances in therapy for these microorganisms have not kept pace with improved diagnosis.

CURRENT PERSPECTIVES

Blood Cultures

Excellent recent reviews of blood culture methods from the clinician's perspective are available (12, 256, 338). The following comments are intended only as a brief overview. Because there is no standard for determining the presence or absence of bloodstream infection, the true sensitivity and specificity of blood cultures can only be estimated (12). There seems to be near-uniform consensus that one set of blood cultures rarely suffices, and therefore two or three sets are commonly recommended. While 30 ml may be the optimum volume of blood to culture (338), two sets of cultures using 10 ml of blood per set should suffice for most purposes (244). Definition of the optimum volume of blood to culture is especially problematic in newborn infants (242). Obtaining blood samples through an arterial catheter is not a reliable substitute for the conventional venipuncture technique (326).

No single blood culture system is ideal for all purposes (338). For example, the lysis-centrifugation method allows both increased and also more rapid detection of most aerobic and facultatively anaerobic bacteria and also of fungi but seems less efficient for detecting pneumococcal and anaerobic bacteremias compared with conventional systems (338). The use of a second or backup system is recommended, especially when the clinical findings are consistent with subacute or chronic endocarditis due to one of the more fastidious microorganisms. It may be useful for laboratory personnel to publicize to medical staffs from time to time which blood culture systems are "routine" and which are available by special request. If the full potential of the newer, more efficient systems is to be realized, it is essential not only to maintain good communications with the clinical staff but also to consider reorganizations of the workday shifts (79).

The call for accountability and cost-effectiveness applies to blood culture methods as to everything else in today's medical practice. Some systems, while theoretically desirable, may be cost-ineffective (90). Concern has been expressed that physicians request far too many blood cultures and therefore that protocols should be developed to define what constitutes appropriate use patterns (137). For example, a single blood culture may be adequate in many cases of pneumonia or acute pyelonephritis (244). On the other hand, it has also been suggested that not enough blood cultures are obtained. The finding in one study that house officers failed to obtain blood cultures promptly in 10% of bacteremic episodes prompted the conclusion that "clinical judgment was not an adequate substitute for routinely obtaining blood cultures for febrile medical inpatients" (205). Guidelines for obtaining blood cultures have also been developed for outpatients (191, 204). In all settings, examination of standard peripheral blood smears for "toxic" changes in the patient's polymorphonuclear neutrophils continues to be an important, if underutilized, basis upon which to make such decisions. In highly select circumstances, examination of buffy-coat smears for microorganisms may also be useful (200, 273).

Presumptive and Precise Antimicrobial Therapy

Physicians request blood cultures when clinical symptoms or signs raise the possibility of infection. When evidence of infection is unequivocal, presumptive antimicrobial therapy is usually initiated. Often, however, patients do not have clear-cut symptoms or signs pointing to either localized or systemic infection. Especially among hospitalized patients, fever can be due to causes other than infection (110). The physician then faces a familiar dilemma. On the one hand, broad-spectrum antimicrobial therapy may improve the prognosis of an infection, if present. On the other hand, antimicrobial therapy increases the cost of medical care, the risk of complications, and the potential for further diagnostic confusion. The clinician must decide whether to prescribe presumptive (or empiric) antimicrobial therapy or to observe the patient's course while awaiting the results of laboratory studies. Positive blood cultures often enable the clinician

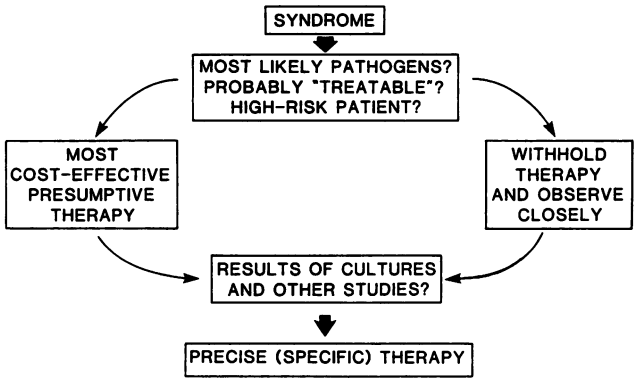

FIG. 3. Algorithmic approach to presumptive and precise antimicrobial therapy (from reference 47, with permission).

both to certify the diagnosis and to prescribe specific therapy based on in vitro susceptibility data (Fig. 3).

Most laboratories now provide clinicians with tabulated antimicrobial susceptibility patterns of commonly isolated microorganisms. These data, especially when pertaining to blood isolates, enable clinicians to make rational decisions for presumptive therapy. For routine susceptibility testing, today's laboratories must choose among numerous effective antimicrobial agents. These choices influence clinicians' prescribing patterns and should therefore be made in consultation with representatives from the medical staff, the pharmacy, and the infection control department.

Recently introduced antibiotics enhance the ability of the clinician to provide safe and effective antimicrobial therapy for most patients. The ideal agent for presumptive therapy should be active against all potential pathogens, should have favorable pharmacokinetics, and should be nontoxic. For bacterial infections, imipenem approaches this ideal, although it lacks activity against a handful of bacteria, including methicillin-resistant *S. aureus* strains. Other useful agents for presumptive therapy with wide therapeutic indices (that is, the therapeutic blood level/toxic blood level ratio) include the newer cephalosporins, ampicillin-sulbactam, ticarcillin-clavulanic acid, and the fluorinated oxyquinolones. Unfortunately, hospital practice gives daily reminders that broad-spectrum presumptive therapy predisposes patients to colonization and superinfection by pathogens more difficult to treat, including fungi. Therefore, it is usually desirable to simplify therapy after a brief period of broad-spectrum presumptive coverage.

In 1977, Young et al. proposed the "rules of three," based on the premise that nearly all instances of bacteremia will be recognized after the incubation of three blood cultures for 3 days (369). Hence, therapy should be reevaluated at 3 days, since thereafter the likelihood that the blood cultures will become positive progressively diminishes (22, 369). Simplification of therapy at that time can be based on the results of blood cultures, the clinical course of the patient, or both. Newer rapid detection blood culture systems should enable us to modify the axiom of rules of three. In one study, only 4 of 268 specimens were found to be positive subsequent to the second day of incubation, and in each of these cases there was an identified source of infection (280). Hence, use of improved blood culture systems might enable us to formulate the "rules of two" (incubation of two blood cultures for 2 days) or, perhaps someday, even the "rule of one." Also, rapid blood culture methods used in conjunction with direct automated susceptibility tests provide accurate presumptive information (287). When simplifying therapy, the clinician should consider the possibility that microorganisms requiring longer incubation periods, such as anaerobic or fastidious bacteria, mycobacteria, and fungi, might be present. The clinician should also recognize that syndromes characteristically of polymicrobial origin often require continued broad-spectrum therapy even when cultures show a single pathogen. The isolation of enterococci or anaerobic bacteria often signifies polymicrobial infection even when this is not apparent from the blood cultures.

Similarly, the possibility for safe and effective specific therapy for most patients has been enhanced by the recent introduction of aztreonam. Aztreonam, which is clinically active only against infections caused by aerobic gram-negative bacteria, completes a triad of agents with selective (or restricted) spectra of activity against pathogenic bacteria. The other members of this triad are vancomycin and metronidazole, which have selective activities against gram-positive bacteria and anaerobic bacteria, respectively. Thus, it is now possible to prescribe therapy specific for aerobic gram-negative, gram-positive, or anaerobic infection without suppressing other components of the body's normal bacterial flora.

In choosing specific antimicrobial therapy against a microorganism isolated from blood cultures, clinicians must also estimate the desired "kill ratio": that is, the ratio of the drug's blood or tissue antibiotic concentrations to the minimum inhibitory concentration against the pathogen. Blood isolates should be saved so that this ratio can be measured, when indicated, by the serum bactericidal test (265, 316). Routine use of the serum bactericidal test should be discouraged, since the kill ratio can usually be approximated by knowledge of the pharmacokinetics of the drug and its minimum inhibitory concentration against the infecting microorganism (317). Situations in which the serum bactericidal test is especially indicated, however, include endocarditis, osteomyelitis, and septicemia due to pathogens difficult to eradicate in immunocompromised patients. Limited data suggest that serum bactericidal titers exceeding the customary eightfold kill ratio may be clinically advantageous (347).

Future Directions

Future generations may look back on blood cultures and antimicrobial therapy as halfway technologies. Already, a variety of non-culture-dependent methods for demonstrating bacteremia or fungemia exist. These include microscopy with specific staining, physicochemical demonstration of antigens, and obtaining indirect evidence of the presence of an organism by showing its bioactivity. Such antigen detection methods as counterimmunoelectrophoresis and latex agglutination are now widely available, although results have been mixed at best (3). The enzyme-linked immunosorbent assay is especially promising (10). Refinements of the *Limulus* assay for endotoxin may enable physicians to exclude the presence of gram-negative septicemia (329). We can anticipate that someday a "microbial detection system" will screen blood specimens for all known microorganisms and thus eliminate the need for presumptive (as opposed to precise) therapy.

We can also expect a host of new strategies that will offer rapid counteraction of the effects of septicemia. The newfound ability to make monoclonal immunoglobulins against virtually any antigen should simplify the problem of toxin neutralization. New approaches to drug therapy should

similarly neutralize the damage done by physiologic accomplices to the "systemic septic response." Physical removal of microbes from the bloodstream, as opposed to killing the microbes with drugs, is already being discussed (213). Yet the ultimate strategy will always be prevention. New insights into the molecular basis for the host-parasite relationship, especially those pertaining to the microbial adherence phenomenon, hold great promise.

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