Changing Patterns of Infections and Antimicrobial Susceptibilities

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Nosophomial bloodstream infections across the United States and in Europe are increasingly attributable to gram-positive species—a trend that represents a reversal of the gram-negative predominance of the previous patterns.

Introduction

Patients with hematologic malignancies and other patients with cancer who are receiving aggressive treatment with chemotherapeutic regimens are highly susceptible to infections because of lowered leukocyte counts and breakdown in their mucosal and immunologic barriers.[1] These patients often experience episodes of fever and neutropenia, and are hospitalized to receive intravenous antimicrobial therapy until their acute illness resolves. The appropriate choice and prompt delivery of antibacterial drugs is crucial to decrease morbidity and mortality in these patients.

Selection of empiric treatment for any bacterial infection must account for antibiotic resistance patterns. The kinds of organisms that predominate vary geographically, temporally, between patients, and within the same patient over time.

The predominant infectious organisms in patients with neutropenia and fever have shifted over the past few decades: gram-negative bacilli were more prevalent in the past, but gram-positive cocci now predominate. This shift in pathogens is one of several factors that must be taken into account in the design of an effective empiric drug regimen.

This article will review changes in the prevalence of bacterial species causing bloodstream infections in the United States and Europe. The article will also review microbial resistance patterns and present evidence regarding newer drugs that are active against resistant bacterial strains. Data from microbiologic surveys in institutions that treat cancer patients are considered, along with surveillance data of bloodstream infections among the general hospitalized population.

Emergence of Gram-Positive Bacterial Predominance

The pattern of isolates causing bloodstream infections in hospitalized patients, both in the United States and in Europe, has changed, and gram-positive organisms are now predominant. The investigators conducting the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE), a national surveillance program, recently reported findings from 10,617 cases of nosocomial bloodstream infections at 49 hospitals in the United States.[2] For all patients and hospital departments combined, well over half (64%) of the isolates were gram-positive cocci (Table 1).

The most common isolates were coagulase-negative staphylococci, followed by Staphylococcus aureus, and then enterococcus species. Streptococcal species accounted for about 6% of all bloodstream isolates, of which half were due to the viridans group (especially Streptococcus mitis, Streptococcus sanguis, and Streptococcus salivarius).[3] Gram-negative bacilli were isolated in 27% of these samples. This is a reversal of the pattern of the organisms recovered in the 1970s, when gram-negative species were isolated in more than 75% of nosocomial bloodstream infections. The pathogens reported in the SCOPE study were from clinically ill patients with bloodstream infections. An analysis of patient subgroups revealed that, among neutropenic patients, S aureus was isolated less often, and streptococci of the viridans group were identified more often, than in patients with a normal neutrophil count.[2] There was also a clear difference in the frequency of specific pathogens when data were subdivided into cases from intensive care units (ICUs) and other inpatient wards (Figure 1).

For example, Enterobacter species (gram-negative) were nearly twice as common in ICUs than in...
regular wards, but the reverse was true for *Escherichia coli* and viridans group streptococci. These observations are a reminder that patterns of pathogens vary among patient subpopulations and hospital departments.

Similar trends have been seen at Memorial Sloan-Kettering Cancer Center (MSKCC), a hospital (approximately 18,000 admissions/year) in New York City that specializes in cancer. Data have recently been compiled that describe the prevalence and resistance patterns of bacteria among all cancer patients, most of whom had leukemia or lymphoma or were recipients of a hematopoietic stem-cell transplant. Some of the findings in this pool of patients parallel those of the SCOPE study, while others reflect local variation.

A basic finding at MSKCC was that the rate of bloodstream infection cases had increased over the past decade, despite increased prophylactic use of fluoroquinolones and other antibiotics. When the number of specific organisms was analyzed, gram-positive species were detected in blood samples from patients with bloodstream infections more frequently than were gram-negative bacteria (Figure 2). While gram-negative infections have decreased, they still pose a significant potential threat of morbidity and mortality for immunocompromised patients.

The bacterial species most likely to cause infections at MSKCC were coagulase-negative staphylococci, *S aureus*, and enterococci. Coagulase-negative staphylococci outnumbered *S aureus* by about 400%. Among gram-negative species, *E coli*, *Klebsiella species*, *Pseudomonas aeruginosa*, and *Enterobacter* species were still the most common pathogens, accounting for about 44%, 28%, 16%, and 12% of gram-negative infections, respectively.

### Shifting Pathogen Prevalence in Europe

As in the United States, many European centers are experiencing a rise in the prevalence of gram-positive bacteria and a relative decline of gram-negative species. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) has for decades recorded patterns of infectious microbes among cancer patients entered into their treatment trials.[4] In the 1970s, gram-negative species accounted for about 70% of single-organism bloodstream infections, but by the late 1980s, gram-positive bacteria had become predominant. Currently, gram-positive bacteria account for about 70% of bloodstream infections in these patients (Figure 3).

It should be noted, however, that gram-negative organisms (eg, *P aeruginosa*) are still common enough to require an empiric regimen that includes antibacterial activity against such species. As is the case in the United States, coagulase-negative staphylococci were the most common pathogens, but the prevalence of viridans group streptococci varies between individual centers, and also has varied over the years recorded by the EORTC (Figure 4). For example, in a survey conducted in France with the support of the Maurice Rapin Institute, a low incidence of viridans infection (4% of total cases of febrile neutropenia) was noted, contrary to some other institutions.[Ribaud P. December 1999. Unpublished data.]

### Pediatric Cancer Populations

Pediatric cancer patients who are neutropenic typically experience fever of unknown origin. The populations of suspected causative organisms display several features similar to those of adult populations. In children, as in adults, a predominance of gram-positive infections has been reported in several recent series, both in the United States[5] and Europe.[1,6,7] Coagulase-negative streptococcal species are a common cause of infection.

The Rainbow Babies and Children’s Hospital in Cleveland, Ohio, recently reported infection rates among their leukemia/lymphoma and solid tumor patients.[5] Eighty-three percent of patients developed infections. Bloodstream infections and otitis media were the most prevalent infections, each accounting for 23% of all cases. Gram-positive organisms dominated the blood culture isolates (49%) compared to gram-negative species (34%). Coagulase-negative staphylococci were the predominant gram-positive species.

Mortality due to all causes was 36% in these pediatric patients, one-fifth of which was attributed to infection, particularly gram-negative bloodstream infections.[5] A recent analysis of pediatric blood isolates from an Italian transplant center reported a suspected infection (fever during the granulocyteopenic period) in 87% of patients, with bloodstream infections being the most common type of infection. Gram-positive species were isolated more than twice as often as gram-negative species.[1] Almost all gram-positive species were either coagulase-negative staphylococci or viridans group streptococci.

The frequency of isolates of viridans group streptococci varies widely among reports for pediatric cancer patients at different centers. A pediatric oncology department in Germany found viridans streptococci to be more common than coagulase-negative isolates among leukemia/lymphoma...
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Antimicrobial Resistance
The increased incidence of gram-positive infections has been attributed to the development of resistance to the standard antimicrobial agents used. Resistant organisms have spread effectively among patients, institutions, and communities. Resistance mechanisms are varied and may reside on either bacterial chromosomes or on mobile genetic elements such as plasmids, transposons, and integrons.[8] An important consideration is that interspecies recombination can occur, in some cases resulting in transfer of resistance from one organism to another.[9,10]

Antimicrobial Resistance Patterns In The United States
Surveillance data of bloodstream isolates from hospitalized patients in the United States reflect the well-recognized trend toward increasing antimicrobial resistance among nearly all categories of pathogens. The SCOPE study determined the resistance rates for the bacteria most often isolated in patients with bloodstream infections (coagulase-negative Staphylococcus, S aureus, enterococci, and viridans group streptococci).

Methicillin resistance among the coagulase-negative staphylococci was 80%, although vancomycin resistance was negligible (0.2%).[2] The study reported a 29% incidence of methicillin resistance among strains of S aureus across the nation—twice the rate of 2 decades ago. Staphylococcal resistance to penicillin and resistance to penicillinase-resistant penicillins (oxacillin and nafcillin) is widespread, but still varied, between institutions.

In the United States, 25% of bloodstream infections caused by S aureus are oxacillin-resistant, while S aureus isolates in hospitals in Rome showed an increase in oxacillin resistance from 39% during the 1980s to 69% by 1990.[11] Horváthova and colleagues[12] demonstrated that cancer patients with coagulase-negative staphylococcal infections resistant to methicillin had higher attributable mortality than methicillin-susceptible patients (12% vs. 3%, P < .05). These findings accentuate the problem of bacterial resistance among staphylococci in patients with cancer.

Limited treatment options and interest in reducing glycopeptide selection pressure on gram-positive bacteria have encouraged the use of alternate antimicrobial agents, such as fluoroquinolones.[13] However, studies have shown a significant increase in resistance to ciprofloxacin (Cipro) in oxacillin (Bactocil)-resistant strains of S aureus.[11] The clinical relevance of fluoroquinolone resistance was shown when a randomized study of pefloxacin vs teicoplanin (Targocid) was terminated due to the development of pefloxacin resistance in S aureus and coagulase-negative staphylococci.[14]

Resistance of enterococcal strains to vancomycin emerged in the late 1980s, and vancomycin-resistant enterococci (VRE) are now important nosocomial pathogens. Resistance differs, with 3% of Enterococcus faecalis and 50% of Enterococcus faecium being resistant to vancomycin. However, E faecalis accounted for twice as many infections as E faecium in the SCOPE population.[2]

Antimicrobial resistance has emerged as a concern in viridans group streptococci, especially among immunocompromised patients.[15,16] A recent analysis showed high rates of resistance in 352 unselected blood culture isolates from U.S. medical centers collected from 1993 to 1994. High-level penicillin resistance (minimum inhibitory concentration [MIC] ≥ 4 mg/µL) was observed in 13.4% of the strains and intermediate level resistance (MIC 0.25-2.0 mg/µL) was seen in 42.9% of the strains.[17]

A high level of erythromycin resistance (39.4%) was also seen in streptococcal bloodstream infections in patients with neutropenia.[18] The isolates that were resistant to erythromycin were also resistant to the newer macrolides. Quinolone (23%) and tetracycline resistance (39%) are also common in patients who experience bloodstream infections with viridans streptococci.[19]

All prevalence and resistance data indicate a geographic variation when analyzed by region of the country. For example, 63% of E faecium in northeastern U.S. hospitals were vancomycin-resistant, whereas 32% were resistant in the northwest. Rates of methicillin-resistant S aureus ranged from 38.5% in the southeast to 14.5% in the northwest. Rates of resistance also differed among hospital departments.[2]

Antimicrobial Resistance in Europe
Antimicrobial susceptibility patterns reported from Europe, like the United States, indicate an emerging problem among those pathogens most prevalent in hematologic cancer patients. For example, coagulase-negative staphylococci have acquired resistance to many classes of antibiotics in cancer patients in Norway.[20] Resistance of S aureus to oxacillin is increasing, with 70%
resistance being reported among strains that are also resistant to several other antibiotics. [11] However, most of these strains are susceptible to glycopeptides. Estimated penicillin resistance among viridans group streptococci from a series of neutropenic cancer patients in Spain grew from zero to 57% over a 6-year period, reflecting the trend observed for this organism in the SCOPE study in the United States. [21]

Vancomycin-resistant enterococci are emerging in Europe but currently are not as prevalent as in the United States. [22] Nevertheless, a 41% resistance rate has been reported for enterococcal strains in cancer patients with neutropenia in a Spanish hospital in which no resistance was detected 5 years earlier. [23] In Europe, vancomycin resistance has been attributed to the widespread practice of adding a glycopeptide (avoparcin) as a growth promoter in animal feed. [23, 24]

Such exposure of animals to the antibiotic is likely responsible for the appearance of glycopeptide-resistant strains in the community setting. [24] Since the use of avoparcin in animal feed was abandoned in 1997 in Italy, a decrease from 14.6% to 8% in the frequency of VRE (vanA gene expression) from poultry samples has been reported. [25]

**A Worldwide Trend in Pathogen Shift?**

The shift to a gram-positive-dominated etiology among cancer patients is not restricted to the United States and Europe. Institutions in areas as widespread geographically as Japan, [26] Argentina, [27] and Australia [28] report more gram-positive isolates from bacteremic cancer patients than gram-negative isolates.

It may be too early to conclude that the same trends are emerging around the globe, but the shifts in both the microbial etiologies of bloodstream infections and antimicrobial resistance rates may be indicative of common treatment strategies that ultimately favor species that are ubiquitous (such as coagulase-negative staphylococci), or have a colonization advantage over antimicrobial drug-sensitive species.

**Factors Underlying Changes in Pathogen Populations**

There are multiple causes underlying a shift toward a predominance of gram-positive species in cancer patients. The routine use of indwelling central venous catheters, which provide an entry route for skin bacteria or for those pathogens that might contaminate intravenous (IV) infusates, is important. The pathogens most often responsible for catheter-related infections are gram-positive cocci that are common components of skin flora (S aureus, coagulase-negative staphylococci). [29, 5, 30] An increase in gram-positive bacteria, believed to originate from enteric sources rather than from the catheter site, has been observed. [31]

Other factors that influence the composition of microbial populations include the health of the host's defense mechanisms (skin and mucous membrane integrity; leukocyte count), exposure of the patient to nosocomial pathogens (in ICUs and wards), and biological features of the pathogen, such as its virulence in the host and its antimicrobial susceptibility.

Antimicrobial resistance is a complex and dynamic phenomenon that can be associated with prior antimicrobial exposure. Such resistance can occur because of the ability of bacteria to exchange antimicrobial-resistance genes, both within and between species. Several studies have found a correlation between prophylactic antibiotic use and an increase in pathogen resistance, or have documented the acquisition of strains resistant to a drug in patients who recently had been treated with that agent. [22, 32, 33]

Enterococci are isolated more often after use of cephalosporins and quinolones (often used to treat gram-negative infections), to which the organisms exhibit an inherent high level of resistance. [24] The emergence of resistance is multifactorial and we are only just beginning to understand the interplay of drug-prescribing practices and resistance emergence.

**Microbial Susceptibilities to Newer Drugs**

In a continual effort to control infection, new antimicrobial agents are being developed, and some newly developed agents have favorable resistance profiles. Some of these are structurally related to antibiotics that are in current use and others represent new agents with novel mechanisms or sites of action.

Quinupristin/dalfopristin (Synercid), the first streptogramin antimicrobial, is a combination agent that has inhibitory activity against a broad range of gram-positive bacteria. [33] Inhibitory activity has been observed against staphylococci (regardless of methicillin resistance), viridans group streptococci, and variably against E faecium. [34] A role for quinupristin/dalfopristin in patients with infections due to multiple antibiotic-resistant bacteria was indicated by a study that analyzed 3,653
Clinical isolates.\[35\] High- and intermediate-penicillin-resistant streptococci, methicillin-resistant \textit{S aureus}, and vancomycin-resistant \textit{E faecium} samples showed a narrow range of MIC with quinupristin/dalfopristin and no isolate had a MIC greater than 4 mg/µL.\[35\] Considerable in vitro data exist, supporting the inhibitory activity of quinupristin/dalfopristin against \textit{S aureus} and coagulase-negative staphylococci, including multidrug-resistant strains.\[36\] In clinical trials involving 1,193 bacteriologically evaluable patients, a successful clinical response occurred with quinupristin/dalfopristin in 57.1% to 85.2% of patients.\[37\]

Quinupristin/dalfopristin has also demonstrated in vivo activity against erythromycin-susceptible and intermediate resistant viridans group streptococci.\[18\] Blood culture isolates obtained from patients with neutropenia and fever were analyzed for antimicrobial susceptibility. A high level of erythromycin resistance (39.4%) and intermediate (12.1%) and high-level (24.3%) penicillin resistance was observed. All macrolide antibiotics tested demonstrated cross-resistance to erythromycin, although cross-resistance with quinupristin/dalfopristin was not observed.\[18\]

In vitro activity for quinupristin/dalfopristin against isolates of vancomycin-resistant \textit{E faecium} has been reported to be good, inhibiting 86.4% of the strains at concentrations ≤ 1 mg/µL and 95.1% at concentrations ≤ 2 mg/µL.\[38\] Despite in vitro activity against vancomycin-resistant enterococci, resistance to quinupristin/dalfopristin may develop rapidly.\[39\]

**Linezolid Shows Promise**

Another promising new drug is linezolid (Zyvox), an oxazolidinone recently approved by the US Food and Drug Administration (FDA). Oxazolidinones are a new class of antibacterial agents that are chemically unrelated to available antibiotics.\[40\] Linezolid binds to the 50S ribosomal subunit, resulting in selective inhibition of bacterial protein synthesis.\[41\]

Two studies have shown strong in vitro activity for linezolid, including activity against resistant bacteria.\[40,41\] Analysis of gram-positive isolates showed MICs from 0.5 to 2 mg/mL for staphylococci, pneumococci, and streptococci and a MIC of 4 mg/mL for enterococci.\[40,41\] The activity of linezolid was comparable to vancomycin for all vancomycin-susceptible enterococci, staphylococci, and streptococci.\[40\] Linezolid was the most active agent tested against oxacillin-resistant staphylococci and vancomycin-resistant enterococci.\[40\]

VanA and VanB phenotype vancomycin-resistant enterococci were both inhibited by linezolid at a MIC between 2 and 4 mg/µL. Linezolid also showed potent activity against isolates of \textit{E faecalis} and \textit{E faecium} and was the most active of all agents for \textit{E faecium}.\[40\] The lack of cross-resistance and the potent activity of linezolid indicate that it has the potential to be a major advance in the treatment of gram-positive infections.

Glycylcyclines represent a new member of the tetracycline antibiotic class and are broadly active against gram-positive and gram-negative bacteria, including some antibiotic resistant strains.\[42\] Glycylcycline derivatives have shown activity against both types of tetracycline-resistant bacteria, those that have ribosomal protection and those with efflux pumps.\[8\] Vancomycin-resistant enterococci, multiple-antibiotic-resistant \textit{E faecalis}, methicillin-resistant \textit{S aureus}, and penicillin-resistant \textit{S pneumoniae} were all susceptible to glycylcyclines. Similarly, a new derivative, 9-t-butylglycylamido derivative of minocycline (TBG-MINO), has potent activity against bacterial isolates that exhibit both forms of tetracycline resistance.\[42\]

The in vivo protective effects of this antibiotic were studied in mice that had received acute lethal injections of \textit{E coli}, \textit{S aureus}, and \textit{Strepto-coccus pneumoniae}.\[8,42\] Intravenous administration of this glycylcycline was protective against the same strains that showed in vitro susceptibility.\[42\]

Similar studies with other glycylcycline derivatives showed potent activity against acute lethal infection in mice against \textit{S aureus}, including methicillin-resistant forms, and against penicillin-resistant \textit{S pneumoniae}.\[8\] These findings suggest that the new derivatives of tetracycline that have potent antibiotic activity may provide additional tools in overcoming bacterial resistance. New representatives of the macrolide/ketolide class and the carbapenems are also under development.

**Conclusions**

In the United States and Europe, gram-positive cocci are increasingly responsible for bloodstream infections in both the general hospitalized population and among cancer patients. Coagulase-negative staphylococci are the most common causative pathogen. Viridans group streptococci, previously unusual pathogens, are emerging in several centers as an important cause of bloodstream infections in patients with cancer and neutropenia. Gram-negative microbes have not
disappeared and still cause infections with sufficient frequency to require that empiric treatment cover a wide range of such bacteria. Antibiotic resistance has continued to increase over the past decade. In general, the problem appears greater among the neutropenic cancer population in the United States than in Europe, although the widespread use of glycopeptides in animal feeds may accelerate the resistance problem in Europe.

Antimicrobial drugs are powerful tools that will continue to provide the foundation of treatment for patients with compromised immunity. Judicious use of antimicrobial agents in combination with effective infection control practices to minimize exposure and pathogen spread will contribute to greater patient safety and improved outcome. In patients who are immunocompromised, such as those with hematologic malignancy or those undergoing intensive cytotoxic/radiation therapy and/or hematopoietic stem-cell transplantation, drug-resistant bacteria appear commonly and remain difficult to treat. Diverse mechanisms of resistance exist and the presence of resistance genes on mobile genetic elements suggests that bacterial adaptability will continue to be an important issue. Several new antibiotics are available that appear to have activity against resistant bacteria. Resistance to these newer agents can be expected to emerge eventually. The need for pharmacologic support of immunocompromised patients requires that additional antimicrobial agents with yet new (and preferably multiple) mechanisms of action continue to be developed. Such drugs are in clinical trials currently, and, if used wisely, their availability can offer a continued edge over bacteria for the future. Knowledge of microbial resistance patterns among cancer patients will aid clinicians in designing effective therapeutic regimens.

References:


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