Challenges in the Treatment of Infections Caused by Gram-Positive and Gram-Negative Bacteria in Patients with Cancer and Neutropenia

Kenneth V. I. Rolston
Department of Infectious Diseases, Infection Control and Employee Health, M. D. Anderson Cancer Center, University of Texas, Houston

Infection is the most common complication of chemotherapy-induced neutropenia. Bacterial infections predominate during the early stages of a neutropenic episode, whereas invasive fungal infections tend to occur later. The epidemiological pattern of bacterial infection continues to evolve globally and locally at the institutional level, as do patterns of susceptibility and resistance. These trends are often associated with local treatment practices and have a significant effect on the nature of empirical antibiotic therapy. The increasing rates of antimicrobial resistance among both gram-positive and gram-negative pathogens isolated from patients with neutropenia are posing new challenges. These challenges are compounded by the fact that relatively few new drugs are being developed, particularly those that treat resistant gram-negative organisms. They also stress the increasing importance of prevention and control of infection and stewardship of antibiotics as strategies in the overall treatment of patients with febrile neutropenia. The recognition of a subset of low-risk patients with neutropenia has created new opportunities (e.g., outpatient and oral therapy) and new challenges (e.g., infrastructure, safety, and compliance). These challenges may be met, to some extent, by appropriately adapting national guidelines to local and institutional circumstances.

Bacterial infection continues to be the most common complication of chemotherapy-induced neutropenia [1, 2]. The goal of antineoplastic therapy is to achieve maximum antitumor responses, which usually result in substantial and, sometimes, prolonged neutropenia. Recent advances in supportive care have made it possible for oncologists to be increasingly aggressive in pursuit of this goal. With the development of new drugs, technologies, and other modalities and protocols for treating cancer, new challenges in the treatment of patients with febrile neutropenia have emerged. This article will focus on current challenges associated with bacterial infections.

EPIDEMIOLOGICAL CHANGES

The epidemiological pattern of bacterial infection in patients with neutropenia undergoes periodic changes and is influenced by the following factors [3]: (1) the severity and duration of neutropenia, (2) the nature and intensity of antineoplastic therapy, (3) other host-related factors, (4) selection pressures created by the use of chemoprophylaxis and/or empirical antibiotic therapy, (5) the use of central venous catheters and other external medical devices, (6) environmental and geographic factors, and (7) duration of the hospital stay. Detection of these epidemiological shifts in a timely manner is critical for the success of empirical antibiotic therapy, which is a major determinant of survival among patients with neutropenia. This detection requires frequent monitoring and surveillance, especially at institutions treating large numbers of patients with neutropenia, because institutional differences can be substantial, and because reliance solely on national data can be misleading [4–8]. For instance, data from the...
Increasing rates of drug resistance among gram-positive and gram-negative pathogens are being documented in many hospitals, including cancer treatment centers [8, 13, 18, 19, 20]. The most frequently isolated organisms are listed in table 2. Coagulase-negative staphylococci account for 40%–45% of gram-positive infections, and resistance to methicillin among these isolates is 70%–90% [3, 14, 19]. Among *Staphylococcus aureus* isolates, resistance to methicillin has been >50% at many centers. Among *Enterococcus* species, resistance to vancomycin is now >30% [21]. Many of these organisms are multidrug resistant. Approximately 50%–60% of viridans group streptococci and *Streptococcus pneumoniae* are not susceptible to penicillin (MIC, ≥0.12 μg/mL), and ~20% exhibit high-level resistance to penicillin (MIC, >2.0 μg/mL) [19, 20, 22–24]. Gram-positive organisms intrinsically resistant to vancomycin (e.g., *Leucostoc* species, *Lactobacillus* species, and *Pediococcus* species) are being isolated with increasing frequency [3, 13]. Tolerance to vancomycin (minimum bacterial concentration [MBC], ≥32 times the MIC) appears to be frequent among many gram-positive species [25]. All of these factors have made treatment of gram-positive infections a greater challenge than in the past.

Drug resistance has become an important issue for gram-negative pathogens as well. The use of fluoroquinolones for prophylaxis in high-risk patients with neutropenia has been associated with the emergence of resistance among *Escherichia coli* and *Pseudomonas aeruginosa* isolates [26–28]. Resistance to ciprofloxacin among *P. aeruginosa* isolates has been >20% at some institutions [6, 8, 18]. The use of older quinolones (norfloxacin, ofloxacin, and ciprofloxacin) may also have led to the increased frequency of infections caused by drug-resistant, non-fermentative gram-negative bacilli, such as *Alcaligenes* species, *Pseudomonas* species other than *P. aeruginosa*, and *Stenotrophomonas maltophilia* [29]. Rates of extended-spectrum β-lactamase (ESBL)–producing isolates among *E. coli* and *Klebsiella* species are increasing [30]. ESBL–producing *Klebsiella pneumoniae* isolates will render most cephalosporins and some combinations of β-lactam and β-lactamase ineffective [31]. They may also acquire mechanisms of resistance to quinolones and...
Table 2. Common bacterial pathogens in patients with febrile neutropenia.

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive</strong></td>
<td>Increasing rates of penicillin resistance among streptococci; methicillin resistance among staphylococci, vancomycin resistance among enterococci, and vancomycin tolerance among most gram-positive bacteria</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em> species</td>
<td></td>
</tr>
<tr>
<td>Viridans group streptococci</td>
<td></td>
</tr>
<tr>
<td><em>Bacillus</em> species</td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium</em> species</td>
<td></td>
</tr>
<tr>
<td>β-Hemolytic streptococci</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><strong>Gram negative</strong></td>
<td>Increase in ESBL-producing organisms; fluoroquinolone-resistant and multidrug resistant</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella</em> species</td>
<td></td>
</tr>
<tr>
<td><em>S. maltophilia</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
<td></td>
</tr>
<tr>
<td><em>Citrobacter</em> species</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter</em> species</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** ESBL, extended-spectrum β-lactamase.

some aminoglycosides. Resistance of ESBL-producing organisms to the combination of piperacillin and tazobactam has been reported and is of concern [32]. Plasmid-mediated, AmpC-type β-lactamases produce similar patterns of resistance, as well as resistance to some carbapenems [33]. Among *Enterobacter* isolates, resistance to ceftazidime is mediated by a Bush group 1 cephalosporinase and has been >30% [7]. Resistance to carbapenems among *P. aeruginosa* isolates is increasing (15%–20% in some institutions). Some of these isolates are truly multidrug resistant and are susceptible only to such agents as colistin and polymyxin B [34–36]. However, like the aminoglycosides, colistin and polymyxin B have suboptimal clinical efficacy in patients with neutropenia when used as single agents, and need to be combined with other agents (preferably β-lactams) that are active against the offending pathogen [37, 38]. All of these patterns of drug resistance are of concern and must be taken into consideration when prophylaxis and empirical therapy are being considered.

Several methods for reducing problems associated with resistance to existing antimicrobial agents have been recommended (table 3). One strategy consists of maximizing initial empirical coverage with subsequent reduction or streamlining (de-escalation) of the regimen. An example of this strategy is the empirical use of vancomycin, on the basis of current guidelines of the Infectious Diseases Society of America (IDSA), but subsequent discontinuation of vancomycin after ~72 h, on the basis of clinical and microbiologic data [2]. Streamlining of gram-negative coverage may not be possible for patients with severe and prolonged neutropenia.

Another strategy is to restrict antibiotic classes associated with a high risk of promoting multidrug resistance. The widespread use of extended-spectrum (third-generation) cephalosporins has been associated with increased rates of isolation of ESBL-producing and gram-positive organisms, such as vancomycin-resistant enterococci (VRE) [39]. Restriction of this class of antimicrobial agent has resulted in reversal of these trends [40]. Some studies suggest that the use of agents such as piperacillin-tazobactam might actually have a protective effect against infection with VRE [41].

There is evidence suggesting that the frequent use of other classes of antimicrobial agents is also associated with the selection of multidrug-resistant isolates. Examples include the carbapenems, which select for resistant nonfermentative gram-negative bacilli (i.e., *Acinetobacter* species, *P. aeruginosa*, and *S. maltophilia*), and the quinolones, which select for mutants with unregulated efflux pump mechanisms. Although it is not practical to restrict multiple classes of antibiotics in an attempt to reduce the emergence of resistance, 2 other interventions—antibiotic cycling and antibiotic heterogeneity—might be practical alternatives. “Antibiotic cycling” is the scheduled rotation of antibiotics after exclusive use for a preset period (usually 6 months to 1 year) and is based on the concept that removal of an antibiotic from use after a defined period will reduce selection pressures. Early experience with the rotation of aminoglycosides
seemed to favor antibiotic cycling [42]. This favorable trend has not, however, been confirmed by recent experience [43]. “Antibiotic heterogeneity,” on the other hand, supports the equal use of multiple classes of antimicrobial agents (e.g., aminoglycosides, various β-lactams, and fluoroquinolones), as outlined by the various choices offered for empirical therapy for patients with febrile neutropenia in the most recent IDSA guidelines [2]. This strategy has been used successfully at a number of institutions, including the M. D. Anderson Cancer Center; however, studies comparing antibiotic restriction, cycling, or heterogeneity have not been conducted. Consequently, it is difficult to favor one strategy over another.

Strict adherence to infection-control practices can prevent the spread of drug-resistant organisms from one patient to others. These practices include hand hygiene, barrier isolation precautions, and screening for and isolation of specific pathogens, such as VRE and methicillin-resistant Staphylococcus aureus (MRSA).

The Centers for Disease Control and Prevention has outlined a 12-step program for the prevention and management of antimicrobial resistance (“Fact Sheet: 12 Steps to Prevent Antimicrobial Resistance among Hospitalized Adults” [available at: http://www.cdc.gov/drugresistance/healthcare/ha/12steps_HA.htm]). This program is of particular importance in settings (e.g., the intensive care unit) and patient populations (e.g., patients with febrile neutropenia) where the potential for development of resistance is high because of heavy antimicrobial use, because it stresses stewardship of antibiotics and infection control.

TABLE 3. Strategies to reduce drug resistance.

<table>
<thead>
<tr>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited antibacterial prophylaxis</td>
</tr>
<tr>
<td>Targeted therapy (when possible)</td>
</tr>
<tr>
<td>Streamlining (de-escalation) of empirical regimen</td>
</tr>
<tr>
<td>Antibiotic restriction</td>
</tr>
<tr>
<td>Antibiotic cycling</td>
</tr>
<tr>
<td>Antibiotic heterogeneity</td>
</tr>
<tr>
<td>Strict adherence to infection-control policies</td>
</tr>
<tr>
<td>Development of new drugs</td>
</tr>
</tbody>
</table>

PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES

In addition to antimicrobial spectrum and potency, 2 other components of antimicrobial pharmacology are considered to be important: (1) antimicrobial concentrations in the serum and at the site(s) of infection (i.e., pharmacokinetics) and (2) the relationship of the drug concentration to the rate and extent of pathogen killing (i.e., pharmacodynamics). The potency of antimicrobial agents is measured by using susceptibility testing end points, such as the MIC and the MBC. Bactericidal activity may be an important issue, particularly in patients with neutropenia [44]. In one study of such patients with gram-negative bacteremia, a peak serum bactericidal titer of ≤1:8 was associated with therapeutic failure in 83% of episodes, in contrast to a response rate of 87% when the peak serum bactericidal titer was ≥1:16 [45].

Antimicrobial concentrations that result in bacterial killing generally follow 1 of 2 patterns. The first pattern is “concentration-dependent killing”—that is, the higher the concentration, the greater the rate and extent of bacterial killing. Concentration-dependent antimicrobial agents commonly used for treatment of patients with neutropenia include the aminoglycosides and the fluoroquinolones. Dosing regimens for such agents should maximize peak serum concentrations or overall exposure to the drug (i.e., area under the curve). In some cases (e.g., extended-interval dosing of aminoglycosides), larger, infrequently administered doses may be necessary to achieve sufficient concentrations, resulting in faster and more-extensive bacterial killing [46]. Most recent studies evaluating the use of aminoglycoside-containing regimens for patients with neutropenia have used extended interval doses (usually once daily), rather than multiple daily doses [2]. It is important to remember that, for patients with neutropenia, aminoglycosides must be combined with other agents that have gram-negative activity, regardless of the schedule of administration [2, 38].

The second pattern of antimicrobial activity is “time-dependent killing.” Drugs that follow this pattern do not exhibit enhanced killing with increasing peak serum concentrations. Instead, killing is largely dependent on how long the concentration of the drug remains greater than or approximately equal to the MIC. β-Lactam agents exhibit time-dependent killing, and maintenance of drug concentrations greater than the MIC for at least 40%–50% of the dosing interval has been associated with bacteriologic efficacy [47]. These and other pharmacokinetic principles need to be kept in mind when administering antimicrobial agents to patients with febrile neutropenia, either empirically or for documented infections.

RISK ASSESSMENT AND RISK-BASED THERAPY

The administration of parenteral, broad-spectrum empirical antibiotic therapy after hospitalization of patients with febrile neutropenia is the accepted standard of care [2]. This approach is effective (infection-related mortality rate, <10%) but is expensive, labor intensive, and, when applied to all patients with febrile neutropenia, may not represent optimal use of resources [48]. During the past decade, clinical and statistically derived risk prediction rules, which reliably identify low-risk patients with febrile neutropenia, have been developed [48–50]. Using these methods for selection of patients, several groups of in-

Infections in Patients with Neutropenia • CID 2005:40 (Suppl 4) • S249
vestigators have evaluated alternative treatment strategies, including (1) hospital-based oral antibiotic therapy [51, 52]; (2) initial hospitalization, followed by early discharge with parenteral or oral antibiotics [53]; and (3) outpatient treatment of the entire febrile episode with the use of parenteral or oral antibiotics [54–58]. The most attractive option is outpatient treatment for the entire febrile episode, because of several advantages associated with this approach, including decreased costs and a significant reduction in nosocomially acquired superinfections [48]. Careful selection of patients, the use of appropriate (not merely convenient) empirical regimens, and daily monitoring of patients (for response and toxicity) are critical for the success of this novel approach. Some of the requirements necessary for a successful program of outpatient therapy for patients with febrile neutropenia may pose substantial logistic challenges, especially at institutions not accustomed to caring for large numbers of such patients (table 4). These challenges include a dedicated team and availability of support services around the clock, including weekends. Should these services not be available, safety concerns would dictate hospital-based therapy, even for low-risk patients.

Despite the promise of outpatient therapy, several issues need to be further evaluated. There is room for refinement of the various risk assessment strategies, to reduce the misclassification rate (i.e., improving specificity without sacrificing sensitivity). Studies are under way to determine rules to predict the duration of neutropenia, a critical factor in risk assessment [59]. Newer antibiotic regimens, especially for patients who are allergic to quinolones or β-lactams, need to be evaluated, and standard criteria for monitoring patients receiving outpatient therapy need to be established.

DEVELOPMENT OF NEW DRUGS

Of increasing concern to most infectious diseases practitioners and public health officials is the fact that, although rates of drug resistance among bacterial pathogens are increasing, virtually no new antibiotics are being developed [18, 60]. Since 1998, only 2 novel classes of antibiotics (oxazolidinones and lipopeptides) have been approved by the US Food and Drug Administration (FDA; Bethesda, MD). All other approved drugs are improvements on agents with known mechanisms of actions. Furthermore, of the 506 drugs being developed for various ailments, only 6 are antibacterial agents. A significant problem is the need to develop targeted antibiotics with activity against drug-resistant organisms, such as MRSA, VRE, P. aeruginosa, and S. maltophilia. Unfortunately, the market for such drugs is too small to make their development profitable for most pharmaceutical companies. In contrast, broad-spectrum agents that can be used for a large number of indications have a bigger market but also promote the development of resistance. The IDSA considers this state of affairs to be an imminent public health crisis and has urged the federal government to take urgent steps to address the problems of antibiotic resistance and the development of new drugs. Some of the recommendations made by the IDSA include (1) the establishment of a commission to prioritize discovery of antimicrobials; (2) the provision of statutory incentives, such as “wild card patent extension” and tax incentives for pharmaceutical companies; and (3) the creation of liability protections. The full report, which contains specific recommendations for the FDA and the National Institute of Allergy and Infectious Diseases, is available at the IDSA Web site (“Bad Bugs, No Drugs;” http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf). Even with swift action by all the appropriate organizations, therapeutic options for multidrug-resistant organisms (especially gram-negative bacilli) will remain very limited for the next 5–10 years, with increasing reliance on older agents and multidrug combination regimens.

SUMMARY

The treatment of patients with febrile neutropenia has evolved during the past 4 decades. Epidemiological shifts occur periodically and have an effect on antimicrobial prophylaxis and empirical therapy. Although bloodstream infections are common, other sites of infection and polymicrobial infections should not be ignored. Recently developed risk assessment strategies have facilitated the identification of low-risk patients with febrile neutropenia at the onset of a febrile episode. Newer treatment strategies for such patients are being evaluated. The global problem of increasing antimicrobial resistance is beginning to limit therapeutic options for the treatment of resistant bacterial infections in patients with neutropenia as well. Unfortunately, the development of new drugs is not keeping pace

Table 4. Requirements for ensuring a safe and successful outpatient treatment program for patients with febrile neutropenia.

<table>
<thead>
<tr>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional infrastructure and support 24 h/day, 7 days/week (e.g., emergency department, laboratory services, and radiology services)</td>
</tr>
<tr>
<td>Dedicated and experienced team of health-care providers (physicians, nurses, pharmacists, radiologists, and home health-care personnel)</td>
</tr>
<tr>
<td>Availability of institution-specific epidemiological data and susceptibility and resistance data</td>
</tr>
<tr>
<td>Careful patient selection</td>
</tr>
<tr>
<td>Microbiologically appropriate (not merely convenient) treatment regimens</td>
</tr>
<tr>
<td>Frequent follow-up monitoring of outpatients</td>
</tr>
<tr>
<td>Motivated, compliant patients and family</td>
</tr>
<tr>
<td>Adequate transportation and communication capabilities</td>
</tr>
<tr>
<td>Access to management team 24 h/day, 7 days/week (e.g., a hotline number) and reasonable proximity to the primary health-care facility</td>
</tr>
</tbody>
</table>
with the development of resistance. Urgent action is needed to reverse this trend.

Acknowledgments

Potential conflicts of interest. K.V.I.R: no conflict.

References

20. Diekema DJ, Jones RN, Rolston KVI. Antimicrobial activity of gatifloxacin compared to seven other compounds tested against gram-positive organisms isolated at 10 cancer-treatment centers. Diagn Microbiol Infect Dis 1999;34:37–43.
34. Toleman MA, Rolston K, Jones RN, Walsh TR. blacVrN, an evolutionarily distinct metallo-β-lactamase gene in a Pseudomonas aeruginosa


