The Evolution of Antibiotic Therapy for Neutropenic Patients

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Abstract
Considerable progress has been made in the treatment of infections in neutropenic patients during the past three decades. A major contribution to this progress has been the discovery of effective new therapies and their prompt administration. Unfortunately, successful therapy of each important pathogen has resulted in the emergence of new pathogens, usually with unique patterns of antibiotic susceptibility. Unfortunately, antibiotic resistance has become an increasing threat in recent years, raising the possibility of infections that will be difficult to eradicate. Fortunately, there are new classes of antimicrobials that hold promise for therapeutic success in the future.

The infectious complications of cancer patients did not elicit any substantial interest until effective antitumor agents became available. Because acute leukemia was one of the first malignancies for which therapy that produced complete remissions was available and because of the prolonged neutropenia associated with this disease and its therapy, much of the research on infectious complications of cancer patients has focused on this disease.

The early 1960s were an exciting time for those of us working on the Acute Leukemia Service at the National Cancer Institute because of Dr. Emil J Freireich’s stimulating leadership. Already a decade of information on the disease was available, new active agents such as vincristine were undergoing clinical investigation, and Dr. Freireich’s innovative pioneering work on combination chemotherapy was being initiated. However, the promise of high remission rates and prolonged survival was tempered by the high fatality rates during remission induction therapy. Dr. Freireich encouraged several of us to embark on an autopsy review of the causes of death in acute leukemia during the period from 1954 to 1963 (1). This study demonstrated that fat hemorrhage had been substantially reduced with the introduction of platelet transfusions, but infection remained the primary cause of death in about 70% of the cases during this period (Table 1). During the period from 1954 to 1959, penicillin-resistant Staphylococcus aureus accounted for 24% of fatal infections, but this was reduced to 5% during 1960 to 1963, after methicillin became available.

It should be emphasized that the prevailing opinion of many infectious disease experts was that serious infections could not be cured in patients who were neutropenic; therefore, this observation was extremely important. Also, the current dictum was that febrile neutropenic patients should not be treated with antibiotics until a site of infection was definitely identified and preferably the infecting organism as well. A few early papers suggested that empiric antibiotic therapy might be indicated for some leukemic patients with fever. With Dr. Freireich’s guidance and encouragement, the first prospective, randomized trials of therapeutic modalities for fever in leukemia patients were initiated (2, 3). The first trials investigated the use of gamma globulin and adrenal corticosteroids, neither of which proved to be useful but set the stage for the first randomized trial of antibiotic therapy in neutropenic patients (4). These studies introduced the concept of the routine initiation of antibiotic therapy when neutropenic patients became febrile.

Unfortunately, success in the management of S. aureus infections was accompanied by an increasing frequency of Gram-negative bacillary infections, especially those caused by Pseudomonas aeruginosa (Table 1). By the mid-1960s, the standard empiric regimen had become cephalothin plus a polymyxin, but studies at M. D. Anderson Cancer Center demonstrated that polymyxin was essentially ineffective as an antibiotic agent, especially in neutropenic patients, and that the combination was associated with electrolyte abnormalities (5, 6). The overall mortality from Pseudomonas septicemia among patients treated with this antibiotic was 76% compared to 86% among patients treated with inappropriate therapy. Pseudomonas infection caused extensive tissue destruction and rapid death in neutropenic patients. Gentamicin, the first aminoglycoside with anti-pseudomonal activity, was very effective against Gram-negative infections in patients with adequate neutrophils but had little impact on these infections in neutropenic patients. Table 2 illustrates these differences with gentamicin and also another similar aminoglycoside, tobramycin (7, 8). Because many neutropenic patients were also thrombocytopenic, we were the first investigators to administer gentamicin i.v.

The introduction of carbenicillin, the first β-lactam with anti-pseudomonal activity, proved to be a dramatic advance in antibiotic therapy for neutropenic patients (9). Although this agent had only marginal activity against P. aeruginosa in vitro and required a daily dose of 30 g, it was found to be highly effective. Even patients with persistent severe neutropenia had a response rate of over 70% (Table 3). The combination of carbenicillin (and subsequently, other antipseudomonal β-lactams) plus an aminoglycoside became standard empiric therapy for fever in neutropenic patients for many years.

Although the alternative of using carbenicillin plus cephalothin was also found to be an effective regimen at some institutions, the introduction of moxalactam stimulated greater interest in combining a penicillin plus a cephalosporin, because...
different institutions, including a recent trial of ceftazidime or conducted at this institution. Many such trials were conducted at to ceftazidime plus an aminoglycoside, tobramycin, was con-
ceptazidime was as effective as ceftazidime plus piperacillin, 
patients. A comparative trial at this institution demonstrated that the combination of a penicillin plus a cephalosporin was an effective alternative to an aminoglyco-
side-containing combination. This type of combination attracted substantial interest following the introduction of antitumor agents with nephrotoxic potential. The subsequent discovery of the adverse effects of moxalactam on coagulation and the discovery of more potent antibiotics with a broader spectrum of activity led to a decreasing interest in these combinations.

With the introduction of potent broad-spectrum antibiotics, such as ceftazidime and imipenem, it became possible to con-
sider the use of single-antibiotic therapy for fever in neutropenic patients. A comparative trial at this institution demonstrated that ceftazidime was as effective as ceftazidime plus piperacillin, hence eliminating the need for double β-lactam regimens (11).

One of the first trials comparing a single β-lactam, ceftazidime to ceftazidime plus an aminoglycoside, tobramycin, was con-
ducted at this institution. Many such trials were conducted at different institutions, including a recent trial of ceftazidime or imipenem alone compared to the β-lactam plus amikacin (Ref. 12; Table 4). This and most other studies suggested that single- 
agent therapy represented an acceptable alternative to combination therapy, although there were some studies with conflicting results (13).

Although most studies have failed to detect significant differences among various antibiotic regimens, there have been some exceptions. Several examples include one study in which azolocillin was more effective than ticarcillin (14), ceftazidime was more effective than piperacillin (11), and most recently, imipenem was more effective than ceftazidime (12).

Beginning in the mid-1970s, as Gram-negative bacillary infections could be effectively managed, Gram-positive organ-
isms reemerged as significant pathogens. However, many of these organisms were methicillin-resistant, including Staphylo-
coccus epidermidis, Corynebacterium jeikeium, and Bacillus cereus. Factors contributing to this change included more inten-
sive chemotherapy-induced mucositis, extensive use of prophylactic antibiotic regimens that primarily targeted Gram-negative bacilli, and dependence upon indwelling intravascular catheters for drug administration. The frequency of these methicillin-
resistant Gram-positive infections led to the widespread use of vancomycin in initial empiric regimens. Because vancomycin (and in Europe, teichoplanin) was the only effective antibiotic against these organisms, the proper use of this antibiotic became the subject of considerable debate. The empiric use of vanco-
ymycin resulted in many patients receiving the drug unneces-
sarily and raised the possibility of the emergence of vancomycin resistance. Whereas prompt administration of appropriate therapy is critical to successful management of most Gram-negative bacterial infections, it soon became apparent that many of these Gram-positive infections were more indolent. Hence, delays in administration of vancomycin until culture results provided an indication for its use did not have an unfavorable impact on most of these infections (15). Furthermore, a substantial proportion of blood cultures containing S. epidermidis represented contamination and not infection.

Unfortunately, at the present time, although the majority of patients who develop fever while neutropenic can be managed successfully, many institutions have been confronted with the problem of antibiotic resistance. In some instances, the problem has been the emergence of resistance to commonly used antibi-
otics, whereas in other instances it has been the problem of infections caused by new pathogens that are inherently resistant to many antibiotics. As a consequence, unlike earlier times, no single antibiotic regimen is appropriate for all institutions. Rather, physicians must be aware of the predominant pathogens and their antibiotic susceptibility patterns at their own institutions to select appropriate antibiotic regimens.

Infections caused by antibiotic-resistant organisms are more prevalent among neutropenic and other immunocompro-
mised patients for several reasons: (a) patients receiving broad-
spectrum antibiotics for prolonged periods of time are more likely to be colonized and subsequently infected by resistant organisms; and (b) most leukemic patients have indwelling intravascular catheters for prolonged periods that can become contaminated by resistant organisms. Antimicrobial prophylaxis reduces the risk of infection, but when it occurs, it is most likely caused by an organism that is resistant to the prophylactic agent, and often, to other antimicrobial agents. Some antibiotic-resis-
tant organisms are less virulent and thus more likely to cause infection in patients with impaired host defenses.

Several studies have shown that patients exposed to an antibiotic are more likely to be infected by an organism resistant to that antibiotic or related antibiotics in the future. For example, ceftazidime is used widely in regimens for treating fever in neutropenic patients. Recently, ceftazidime-resistant strains of Escherichia coli and Klebsiella pneumoniae have been de-
scribed. At one institution, 11 of the 31 acquisitions occurred in patients who had received ceftazidime or aztreonam previously (16).

At one cancer center between 1988 and 1992, there was nearly a 5-fold increase in the colonization rate of fluoroquin-
olone-resistant E. coli among their leukemic population (17).

Table 1 Causes of death in acute leukemia

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage (%)</td>
<td>67</td>
<td>37</td>
</tr>
<tr>
<td>Infection (%)</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>Septicemia (%)</td>
<td>134</td>
<td>125</td>
</tr>
<tr>
<td>S. aureus (%)</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>P. aeruginosa (%)</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>Fungi (%)</td>
<td>8</td>
<td>23</td>
</tr>
</tbody>
</table>

| Includes disseminated infections.

\[ \text{From Hersh et al. (1).} \]

\[ \text{aeruginosa} \]
is inherently resistant to imipenem, it is not surprising that *Staphylococcus maltophilia* is a common contaminant of implanted devices, from whence it may arise from the respiratory tract and 40% from the gastrointestinal tract (24). In addition to bacteremia, *S. maltophilia* also causes a delay in the acute leukocytosis that is generally assumed that most *S. epidermidis* bacteremias are derived from the skin or intravascular catheters, as many as 20% of these strains produce *β*-lactamases (23). *C. ochraceus* is generally susceptible to clindamycin, imipenem, ciprofloxacin, and broad-spectrum penicillins plus *β*-lactamase inhibitors.

The Gram-positive organism recovered from blood culture specimens most often is *Staphylococcus epidermidis*. Often it is difficult to determine whether this is a pathogen or a contaminant; consequently, it is accepted practice to require two positive blood cultures to diagnose *S. epidermidis* bacteremia. However, in some cases, the organism is only cultured from blood specimens intermittently over a several-day period, increasing the difficulty of discriminating between infection and contamination. Furthermore, because over 50% of strains of *S. epidermidis* are methicillin resistant, they may be isolated from blood specimens during standard antibiotic therapy. *S. epidermidis* is also a common contaminant of implanted devices, from whence it can cause local abscess or seed the bloodstream. Although it is generally assumed that most *S. epidermidis* bacteremias are derived from the skin or intravascular catheters, as many as 20% arise from the respiratory tract and 40% from the gastrointestinal tract (24). In addition to bacteremia, *S. epidermidis* may

<table>
<thead>
<tr>
<th>Initial PMN/mm$^3$</th>
<th>Patients</th>
<th>% cures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>51</td>
<td>75</td>
</tr>
<tr>
<td>&lt;100</td>
<td>16</td>
<td>75</td>
</tr>
<tr>
<td>101–1000</td>
<td>26</td>
<td>88</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>Decreased</td>
<td>29</td>
<td>72</td>
</tr>
<tr>
<td>Increased</td>
<td>22</td>
<td>82</td>
</tr>
</tbody>
</table>

a From Bodey et al. (7).

Table 3 Response of *Pseudomonas* infection to carbenicillin alone related to neutrophil count

In a review of non-*aeruginosa* *Pseudomonas* septicemias, we found that about 30% of 68 patients with *Stenotrophomonas maltophilia* bacteremia developed septic shock, 34% developed pneumonitis, and 16% developed soft tissue infection (21). The cure rate in patients with pneumonia was only 36%, and the cure rate in patients with septic shock was 38%. The successful management of these infections requires the selection of effective antibiotics, and the most appropriate antibiotic may vary at different institutions. Among patients with intravascular catheters, removal of the catheter along with appropriate therapy is critical to successful outcome.

*Capnocytophaga ochracea* is a cause of bacteremia in neutropenic patients with mouth ulcers (22). It is a slow growing *Gram-negative bacillus* that grows anaerobically or in the presence of CO$_2$ *in vitro*. It can be recovered from as high as 30% of throat or sputum specimens. Interestingly, it causes abnormal oral morphology and chemotaxis of neutrophils. It is capable of degrading IgA1 and IgG. At the present time, about 60% of patients with bacteremia have acute leukemia, and 78% have profound leukopenia. Seventy percent of patients have significant oral pathology. The infection is nosocomially acquired in over 50%, and a similar proportion have received prior antibiotic therapy. The mortality rate is about 30%. These organisms are uniformly resistant to vancomycin and aminoglycosides. About 30% of these strains produce *β*-lactamases (23). *C. ochracea* is generally susceptible to clindamycin, imipenem, ciprofloxacin, and broad-spectrum penicillins plus *β*-lactamase inhibitors.

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Table 2 Effect of neutrophil count on response to aminoglycoside therapy of Gram-negative bacillary infections

<table>
<thead>
<tr>
<th>Neutrophil count/mm$^3$</th>
<th>Change</th>
<th>Gentamicin$^a$</th>
<th>Number</th>
<th>% cures</th>
<th>Tobramycin$^b$</th>
<th>Number</th>
<th>% cures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>All</td>
<td>63</td>
<td>52</td>
<td>59</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>All</td>
<td>22</td>
<td>23</td>
<td>21</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>101–1000</td>
<td>All</td>
<td>17</td>
<td>53</td>
<td>10</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>All</td>
<td>24</td>
<td>79</td>
<td>28</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>Decreased</td>
<td>32</td>
<td>31</td>
<td>23</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>Increased</td>
<td>31</td>
<td>74</td>
<td>36</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>Increased</td>
<td>6</td>
<td>33</td>
<td>14</td>
<td>29</td>
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<tr>
<td>&lt;100</td>
<td>Unchanged</td>
<td>16</td>
<td>19</td>
<td>7</td>
<td>14</td>
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<td></td>
</tr>
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</table>

$^a$ From Bodey et al. (7).

$^b$ From Valdivieso et al. (8).
cause pneumonia and serious cellulitis. Of special concern to physicians treating leukemic meningitis is the possibility of Ommaya shunt infection resulting in meningitis, ventriculitis, or brain abscess. Recently, an epidemic of S. epidermidis bacteremia was described on a leukemia and marrow transplant service (25). During a 1-year period, 19 of 49 patients were infected with the epidemic strain. Seven patients had multiple episodes of infection. The strain causing the outbreak was recovered from settling plates placed in multiple sites in the hospital including isolation rooms. This particular strain of S. epidermidis was highly resistant to ciprofloxacin.

For many years, a hemolytic Streptococci were isolated occasionally from blood specimens of febrile neutropenic patients. Because these patients responded promptly to a variety of antibacterial regimens, they were considered to be inconsequential. However, beginning in the 1980s, it became apparent that these Streptococci could occasionally cause serious and even fatal infections, although the majority of infections remain innocuous. Serious infections occur almost exclusively in children and adults with acute leukemia or bone marrow transplant recipients. In one study, 123 of 832 patients undergoing bone marrow transplantation developed α hemolytic Streptococcal bacteremia (26). About 10% of these 123 patients developed symptomatic organ dysfunction, and 10 patients developed a fulminant shock syndrome. Renal failure and acute respiratory distress syndrome are among the serious consequences of these infections and may persist even after the infection appears to be eradicated. Indeed, some of these infections may be so fulminating that the patient expires within several hours after the onset of the first symptoms. Although several Streptococcal species have caused these serious infections, most have been caused by S. mitis and S. sanguis.

Recently, a case-control study of Streptococcus viridans septicemia was conducted at this institution (27). Controls were selected randomly from the group of patients with other aerobic Gram-positive septicemias. Flushing of the face and a rash occurred in nearly 60% of these patients but were uncommon in the control group. The rash was usually erythematous and maculopapular, beginning on the trunk and progressing to the face and extremities. The rash resulted in desquamation of the palms and soles one to two weeks later in 25%. About 10% of the patients developed the acute respiratory distress syndrome, shock, and renal failure and died despite more than 4 days of vancomycin therapy.

Significant differences between the cases of Streptococcal bacteremia and the controls with other Gram-positive bacteria included a higher proportion of the former with oral mucositis, epistaxis, diarrhea, bone marrow transplantation, i.e. alimentation, severe neutropenia (<100/mm3), upper gastrointestinal toxicity, and antacid or H2 antagonist therapy among the cases. In a multivariate analysis, only the last four variables were significant. Recent studies have emphasized that high-dose cytarabine plays an important role in predisposing to this infection and that patients with positive body cultures are at higher risk of infection, but antacids and H2 blockers may be less important predisposing factors than considered previously (28).

The mortality rate from α Streptococcal bacteremia is about 10%, varying from 5 to 30% at different institutions. Optimum therapy for this infection has not been clearly defined. Although strains of S. mitis are susceptible to penicillin G, about 50% of isolates of other species are resistant to, or at least tolerant of, penicillin G. Vancomycin has become the preferred therapeutic agent, but even this antibiotic is not uniformly effective. Antibiotic prophylaxis with penicillin G or oxithramycin has been effective in some centers (29).

Enterococcus faecalis and especially E. faecium have been rare causes of serious infections in leukemic patients in the past. For many years, when such infections occurred, they could be treated with ampicillin alone or in combination with gentamicin. However, in recent years, many strains of Enterococcus spp. have developed resistance to these antibiotics and are only susceptible to vancomycin and teicoplanin (30). Especially disconcerting has been the recent observation that Enterococcus spp. are now causing more serious infections in leukemic patients, including septicemia, meningitis, and pneumonia. Of even greater concern has been the recognition that the recent

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparative trial of ceftazidime versus imipenem with or without amikacin in febrile neutropenic patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftazidime</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>Evaluable patients</td>
<td>182</td>
</tr>
<tr>
<td>Response rates (%)</td>
<td></td>
</tr>
<tr>
<td>Total Episodes</td>
<td>59</td>
</tr>
<tr>
<td>Documented Inf.</td>
<td>49</td>
</tr>
<tr>
<td>Organism Identified</td>
<td>44</td>
</tr>
<tr>
<td>Organism Unidentified</td>
<td>56</td>
</tr>
<tr>
<td>FUO</td>
<td>69</td>
</tr>
</tbody>
</table>

* From Rolston et al. (12).

<table>
<thead>
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<th>Table 5</th>
<th>Potential new approaches to antimicrobial therapy</th>
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</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Mechanisms</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Magainins</td>
<td>Surface electrical charge displaces ions in cell wall, causing holes in cell wall</td>
</tr>
<tr>
<td>Anti-adhesion compounds</td>
<td>Fake receptors that prevent bacterial adhesion</td>
</tr>
<tr>
<td>Penetrations</td>
<td>Protein complexes that carry antibiotics through cell walls</td>
</tr>
<tr>
<td>Cecropins</td>
<td>Antimicrobial peptides from pig intestines</td>
</tr>
</tbody>
</table>
The widespread use of vancomycin has been associated with the emergence of resistance to this antibiotic by some strains of Enterococci.

Unfortunately, infections caused by vancomycin-resistant Enterococci in leukemic and other cancer patients and have been difficult to treat. An outbreak of Enterococcal-resistant bacteremias were identified in an oncology unit during a 1-year period (31). The strain causing these infections was resistant to vancomycin and ampicillin and had high level resistance to aminoglycosides. Of a total of 413 patients admitted to the unit, 167 (40%) were studied to determine if they were colonized by Enterococcus spp. This organism was isolated from stool culture specimens of 29 (17%) of the 167 patients studied. Seven (24%) of the 29 carriers developed Enterococcal bacteremia, and 4 died from their infection. Hence, the potential for untreatable infections occurring among neutropenic patients has again become a reality.

What does the future hold? This paper has focused on bacterial pathogens; certainly because antibiotic-resistant bacteria cause an increasing number of infections, as is most likely to happen, bacteria will continue to be a problem. Perhaps more disconcerting has been the major increase in fungal infections, which happen, bacteria will continue to be a problem. Perhaps more disconcerting has been the major increase in fungal infections, which are more tumor cell-specific would have a dramatic impact. The continuing efforts of basic scientists, clinicians, and the pharmaceutical industry are mandatory. Hopefully, the current reality.

The continuing need for strong infectious disease programs focused on the complex infectious problems of cancer patients if progress in the management of these patients is to continue.

References
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