The Importance of Bactericidal Drugs: Future Directions in Infectious Disease

Robert W. Finberg,1 Robert C. Moellering,2 Francis P. Tally,3 William A. Craig,4 George A. Pankey,5 E. Patchen Dellinger,6 Michael A. West,7 Manjari Joshi,8 Peter K. Linden,9 Ken V. Rolston,10 John C. Rotschafer,11 and Michael J. Rybak12

1University of Massachusetts Medical Center, Worcester, 2Beth Israel Deaconess Medical Center, Boston, and 3Cubist Pharmaceuticals, Lexington, Massachusetts; 4University of Wisconsin, Madison; 5Ochsner Clinic Foundation, New Orleans, Louisiana; 6University of Washington, Seattle; 7Northwestern University Medical School, Chicago, Illinois; 8University of Maryland Medical Center, Baltimore; 9University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; 10The MD Anderson Cancer Center, Houston, Texas; 11University of Minnesota, Minneapolis, Minnesota; and 12Wayne State University, Detroit, Michigan

Background. Although a considerable amount of research has gone into the study of the role of bactericidal versus bacteriostatic antimicrobial agents in the treatment of different infectious diseases, there is no accepted standard of practice.

Methods. A panel of infectious diseases specialists reviewed the available literature to try to define specific recommendations for clinical practice.

Results. In infections of the central nervous system, the rapidity with which the organism is killed may be an important determinant, because of the serious damage that may occur during these clinical situations. The failure of bacteriostatic antibiotics to adequately treat endocarditis is well documented, both in human studies and in animal models.

Conclusion. The bulk of the evidence supports the concept that, in treating endocarditis and meningitis, it is important to use antibacterial agents with in vitro bactericidal activity. This conclusion is based on both human and animal data. The data to support bactericidal drugs’ superiority to bacteriostatic drugs do not exist for most other clinical situations, and animal models do not support this concept in some situations. Clinicians should be aware that drugs that are bacteriostatic for one organism may in fact be bactericidal for another organism or another strain of the same organism.

The importance of bactericidal drugs (which kill bacteria) versus bacteriostatic drugs (which inhibit the growth of bacteria) in the treatment of infections has been debated for many years. Standard in vitro microbiologic assays measure the MIC and the minimum bactericidal concentration (MBC) of an antibacterial agent. The MIC is the concentration of drug that inhibits the growth of bacteria (often measured with a turbidity assay; figure 1). Inhibition of bacterial growth does not necessarily mean that the bacteria have been killed. In vitro bacterial subplating or dilution of bacteria in a growth medium lacking antimicrobial agents may result in bacterial regrowth. In contrast, the MBC is a measure of the concentration at which bacteria are killed by the antibacterial agent.

Bacteriostatic antimicrobial agents, such as sulfonamides, for which the mechanism of action involves blocking a specific metabolic pathway in bacteria (folic acid synthesis), inhibit the growth of susceptible bacteria but do not kill the organisms. Bacterial cultures incubated in the presence of sulfonamides exhibit slowed growth rates, and the organisms stop dividing entirely when exposed to high concentrations of sulfonamides, but when the bacteria are plated in an antibacterial agent–diluted medium or are transferred to growth medium lacking antimicrobial agents, they may resume growth (figure 1).

One clinical measure of antibacterial activity is the serum bactericidal activity test, or Schlichter test [1]. Although it was routinely used early in the antibiotic era, several studies suggested that the serum bactericidal test did not provide substantial, clinically relevant in-
In the case above, the MIC is 2 \text{mg/mL} and the MBC is 4 \text{mg/mL}.
bination may have accounted for the poor clinical outcome in patients treated with both agents (i.e., in vitro addition of a protein synthesis inhibitor may limit the bactericidal activity of a cell wall–active antibiotic). In another study [29], children with meningitis treated with ampicillin monotherapy experienced a 4.3% mortality rate, compared with 10.5% in children treated with a combination of ampicillin, chloramphenicol, and streptomycin.

As striking as these results appear to be, a word of caution is necessary. Although it is generally assumed that the addition of chlorotetracycline to the penicillin regimen led to the dramatic increase in patient mortality, one should be aware that these were small studies and that issues such as patient selection may have been a factor (i.e., patients with more-severe illness might have received combination therapy). In addition, the combination of ampicillin (which is generally bactericidal) and chloramphenicol (which is generally bacteriostatic) was for many years administered as initial therapy for children with meningitis. This regimen may have been successful because most cases of meningitis in children during this period were caused by *H. influenzae* and *S. pneumoniae*, organisms against which chloramphenicol is a bactericidal agent. In addition to whether a drug is bactericidal, pharmacologic considerations, such as penetration into the CSF or activity in acidic environments, are likely to be of paramount importance.

In *Listeria monocytogenes* meningitis, which occurs frequently in immunocompromised hosts, *β*-lactams are usually only bacteriostatic, whereas aminoglycosides, vancomycin, and trimethoprim-sulfamethoxazole are all bactericidal. Ampicillin effectively cleared the CSF in a rabbit model [39], casting doubt on the relationship between bactericidal activity and meningitis treatment. Conversely, when an aminoglycoside was added to the combination, synergistic activity among the agents was noted [39]. Thus, combination therapy is recommended by many clinicians for treating meningitis due to *Listeria* species in immunocompromised patients [40].

In such situations as CNS infection, in which the effects of inflammatory cytokines may be detrimental, the sterilization speed may be more important than it is in other clinical situations. In a study of neonates with meningitis due to gram-negative organisms, the CSF was sterilized more rapidly with cefotaxime than with ampicillin plus gentamicin. There is a large range in the reported mortality for meningitis caused by gram-negative organisms [41, 42]. Although the rapidity with which the bacteria are lysed may be important in clearance, in some cases, lysis of endotoxin-containing bacteria could theoretically be harmful because of the induction of inflammatory cytokines. In a study of the treatment of meningitis due to gram-negative organisms with moxalactam, clinical success or failure could not be discerned on the basis of MICs or MBCs [43]. However, organisms associated with clinical failure demonstrated much slower killing curves, suggesting that the rapidity of killing may be the critical factor in this situation.

## ENDOCARDITIS

Before penicillin, bacterial endocarditis was uniformly fatal. Although sulfonamides were available and led to high cure rates with serious infections, such as pneumonia and septic arthritis, they were not effective in curing endocarditis [44]. When penicillin was first introduced, the cure rate for endocarditis caused by viridans group streptococci was low when total doses of <500,000 U/day of penicillin were administered. After 1946, however, increased penicillin doses led to cure rates similar to those reported today [45, 46]. Initial attempts to treat enterococcal endocarditis with penicillin monotherapy also met with limited success [47, 48]. However, the addition of streptomycin to the penicillin regimen resulted in improved cure rates against enterococci [49, 50]. Because penicillin alone is not bactericidal against enterococci, and because the synergistic combination of penicillin plus an aminoglycoside is bactericidal, these studies suggest that bacterial cures of enterococcal endocarditis require

### Table 1. Bactericidal activity of several classes of antimicrobial agents.

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Bactericidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams and glycopeptides</td>
<td>Inhibition of cell wall synthesis</td>
<td>Yes; see text for exceptions [6]</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Inhibition of DNA replication</td>
<td>Yes [10]</td>
</tr>
<tr>
<td>Macrolides, lincosamides, streptogramins, chloramphenicol, and aminoglycosides</td>
<td>Inhibition of protein synthesis</td>
<td>Aminoglycosides: yes; others: no; see text for exceptions [6, 9]</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Inhibition of protein synthesis</td>
<td>In general, no [14]; may be slowly bactericidal against <em>Staphylococcus aureus</em> [15]</td>
</tr>
<tr>
<td>Polymyxins and lipopeptides</td>
<td>Cell membrane binding</td>
<td>Yes [7, 8]</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>Inhibition of DNA-dependent RNA polymerase</td>
<td>Sometimes [13]</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Inhibition of protein synthesis</td>
<td>No [12]</td>
</tr>
<tr>
<td>Trimethoprim and sulfonamides</td>
<td>Inhibition of folate synthesis</td>
<td>No; see text for exceptions [11]</td>
</tr>
</tbody>
</table>

*Note: The bactericidal activity of certain classes of antimicrobial agents, such as aminoglycosides, may vary depending on the organism and clinical situation. The table provides general information and should be used as a reference. Additional reading is recommended for a comprehensive understanding of the subject.*
a synergistic aminoglycoside in addition to a cell wall–active agent, lending support to the theory that bactericidal activity is critical in this situation [51].

OSTEOMYELITIS

Acute osteomyelitis, an infectious disease usually caused by hematogenous spread of bacteria and predominantly seen in children, has a high cure rate, provided that appropriate antibacterial drugs are given for a long duration. Chronic osteomyelitis commonly occurs in adults, is usually associated with trauma or vascular insufficiency, and, unfortunately, is difficult to cure with antibacterial drugs. The poorly vascularized tissue present in chronic osteomyelitis appears to make penetration by both antibacterial drugs and host cells difficult. Animal models of osteomyelitis suggest no simple correlation between in vitro activity and in vivo efficacy of antibacterial agents. This may be related to the complexity of the pathophysiology (osteomyelitis is a chronic disease in which penetration of antibacterial agents into a relatively avascular, anaerobic environment is thought to be of great importance). In several animal studies, the addition of rifampin to β-lactam drugs resulted in much better sterilization of bone, despite a lack of in vitro evidence of synergy [52, 53].

A small prospective study by Weinstein et al. [25] involving 30 patients with acute osteomyelitis and 18 patients with chronic osteomyelitis tested whether the outcome of an infection could be predicted by a serum bactericidal test, which is a test not commonly used in clinical practice. This small study suggested that bactericidal titers might provide good prognostic information for patients with osteomyelitis, but no large, prospective clinical trials have demonstrated the superiority of bactericidal versus bacteriostatic drugs in the treatment of osteomyelitis.

INFECTIONS IN PATIENTS WITH CANCER

Severely neutropenic patients are likely to rapidly develop overwhelming infection. When administered as single agents, aminoglycosides yielded disappointing results in the treatment of infections in patients with cancer, particularly against documented bacteremia due to gram-negative organisms [54, 55]. The addition of a β-lactam antibiotic to the regimen improved the outcomes of these infections dramatically [56].

During the 1980s, antibacterial agent therapy with combination regimens became standard practice. In some cases—notably, in cases of infection caused by Pseudomonas aeruginosa—clinical outcomes appeared to correlate with synergistic activity of the antibacterial agents administered [57]. In a study of neutropenic patients with bacteremia due to gram-negative organisms [58], a peak serum bactericidal titer of ≥1:16 was associated with clinical success in 87% of patients. In patients with adequate neutrophil counts, a peak serum bactericidal titer of ≥1:8 was associated with clinical success in 98% of patients. The importance of bactericidal titer levels extrapolated beyond a β-lactam and aminoglycoside antibiotic combination is not clear, and animal data on this subject are not convincing.

Clinical studies in the 1980s and early 1990s documented the role of single broad-spectrum β-lactam agents in treating patients with severe neutropenia [59–63]. On the basis of these studies, most clinicians are comfortable with a single cell wall–active agent for initial therapy of infections in neutropenic patients, although most clinicians would administer a combination of a β-lactam and an aminoglycoside in treating a Pseudomonas infection in a neutropenic patient. Nevertheless, no large, randomized, controlled trials have demonstrated that these agents are preferable over other regimens with an equivalent spectrum of activity. A multicenter clinical study with ciprofloxacin was viewed as a failure, predominantly because of the occurrence of bacteremia due to gram-positive organisms, which was predicted in light of ciprofloxacin’s spectrum of activity [64]. The extent of the problem with aminoglycoside penetration of different sites is difficult to determine retrospectively. This is particularly true when a single antimicrobial agent is used to treat a heterogeneous group of infections. Initial studies on the use of single-agent gentamicin in a heterogeneous group of patients with cancer resulted in disappointing outcomes (a 51% success rate) [54]. Many studies involving patients with cancer indicate that the antibiotic agent’s spectrum of activity is important in predicting the outcome of patients who are likely to be infected not only with any one of a wide variety of organisms but, potentially, with multiple organisms. In patients with normal immune responses, some studies have shown that bacteriostatic agents (e.g., trimethoprim-sulfamethoxazole) were superior to bactericidal agents (e.g., ampicillin) in the treatment of urinary tract infections [65, 66]. In these studies, however, the superiority of the bacteriostatic agents was attributable, in part, to the spectrum of susceptible organisms.

Although most recent studies in severely neutropenic patients have been performed with cell wall–active antibiotics, such as ceftazidime and imipenem [67–69], which are usually bactericidal, a number of small case studies have been performed with nonbactericidal agents (which are usually used in situations in which the patient is allergic to β-lactams).

INFECTIONS IN PATIENTS WITH CRITICAL ILLNESS

In patients with S. aureus infections who are treated either with antistaphylococcal penicillins or vancomycin, improved clinical
outcomes are usually attributed to the more rapid bactericidal action of penicillins, compared with vancomycin. Gonzalez et al. [70] reported on a small subgroup of patients with methicillin-susceptible \textit{S. aureus} bacteremic pneumonia in which the mortality rate was 47\% in patients treated with vancomycin, compared with 0\% in patients treated with cloxacinil. Of interest, neither quinupristin-dalfopristin nor linezolid has demonstrated improved outcomes, compared with vancomycin, in other published trials [71–73]. Both quinupristin-dalfopristin and linezolid have the capacity to be either bacteriostatic or bactericidal depending on the organism. Whether the administration of a bactericidal agent such as daptomycin or oritavancin would have better activity in critically ill patients is a provocative question.

One area in which there are data on the issue of bacteriostatic versus bactericidal agents is that of surgical prophylaxis, for which it is clear, in animal studies, that bacteriostatic agents are as effective as bactericidal agents in the prevention of wound infections caused by \textit{S. aureus} [74].

**POTENTIAL DISADVANTAGES OF BACTERICIDAL ACTIVITY**

Although the advantages of bactericidal agents appear obvious (e.g., rapid elimination of bacteria and a decreased possibility of resistance development or infection recurrence), bactericidal activity could be undesirable in some clinical settings. In CNS infection, for example, the sudden lysis of bacteria by a bactericidal agent leads to a sudden increase in bacterial products (e.g., lipopolysaccharide in gram-negative organisms or peptidoglycans in gram-positive organisms) that may stimulate cytokine production, causing potentially harmful inflammation.

The importance of the host response in subsequent damage induced by the infection is suggested by data indicating that the administration of glucocorticoids with antibacterial drugs leads to better outcomes in patients with meningitis [75–78]. When \textit{S. pyogenes} is exposed in vitro to penicillin, high levels of streptococcal pyrogenic exotoxin A are released, compared with the minimal-level release observed when the organism is exposed to linezolid and clindamycin [79]. In toxin-mediated diseases (e.g., toxic shock syndrome), regimens containing protein-inhibitory antibacterial drugs (e.g., clindamycin) may be preferable to regimens using only those antibacterial drugs that target the cell wall, because antibacterial agents that work by inhibiting protein synthesis directly inhibit production of the toxin.

A study of ceftazidime versus imipenem/cilastatin suggests that, under certain circumstances, rapid killing of bacteria may be undesirable [80]. Serum levels of endotoxin increased in 2 of 4 endotoxemic patients with urosepsis receiving ceftazidime, whereas levels of endotoxin decreased in all 3 endotoxemic patients who received imipenem [80]. Although not much can be concluded from such a small clinical study, Prins et al. [80] note that in vitro endotoxin release is much higher from bacteria that are treated with ceftazidime. A similar point was made in an animal study of meningitis [81]. The degree of endotoxin release also appears to be mediated by the specific penicillin-binding protein (PBP) for which the \beta-lactam agent has primary affinity (i.e., endotoxin release is greater following PBP 2 attachment, compared with PBP 3 attachment). As we learn to use more-specific immunomodulators (e.g., TNF and interleukin-1 receptor antagonists), an increasingly attractive strategy would be to consider administering these immunomodulators together with rapidly active bactericidal drugs.

The ability of an antibacterial agent to modulate toxin production is also considered in antimicrobial agent selection [82]. In vitro data indicating that protein synthesis inhibitors such as clindamycin may decrease toxin release by streptococci has led to the suggestion that serious streptococcal infections should be treated with clindamycin. In the case of \textit{Escherichia coli} strains that produce the Shiga toxin, in vitro experiments indicate that certain antimicrobials, including trimethoprim and fluoroquinolones, may actually enhance toxin production. Early clinical data suggested that patients not treated with antimicrobials might have a lower incidence of hemolytic uremic syndrome than those treated with antimicrobials. A recent meta-analysis [83] casts some doubt on the validity of this observation, but the authors noted that the timing of treatment initiation in a patient may be critical to clinical outcome. As we become more sophisticated about early diagnosis of infections and the use of immunomodulators, it may become more important to analyze the effects (i.e., bactericidal or bacteriostatic) of the antibacterial agent on the infecting organism.

**Acknowledgments**

**Financial support.** Cubist Pharmaceuticals.

**Potential conflict of interest.** E.P.T is an employee of Cubist, makers of Daptomycin. All other authors: No conflict.

**References**


67. Bohne A, Shah PM, Stille W, Hoelzer D. Prospective randomized study to compare imipenem 1.5 grams per day vs. 3.0 grams per day in infections of granulocytopenic patients. J Infect 1998; 36:35–42.


