

The Importance of Bactericidal Drugs: Future Directions in Infectious Disease

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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-

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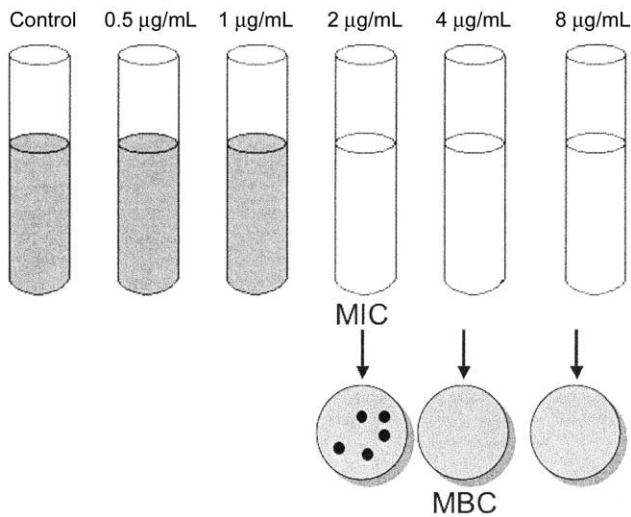


Figure 1. A fixed culture of bacteria is added to each of the 6 test tubes. The first tube serves as the growth control, and no antibiotic is added to this tube. Tubes 2–6 contain antibiotic in serially diluted proportions ranging from 0.5 to 8 $\mu\text{g/mL}$. After 18–24 h of incubation, the first tube that appears visibly clear represents the MIC. However, to determine the minimum bactericidal concentration (MBC), each tube is subsequently plated onto agar plates and incubated. The first serial plated agar dish demonstrating no growth (or a 99.9% decrease) represents the MBC. In the case above, the MIC is 2 $\mu\text{g/mL}$, and the MBC is 4 $\mu\text{g/mL}$.

formation [2–5]. As a result, this test is no longer commonly used in clinical practice.

The continued use of tests to determine antibacterial activity and elucidate the mechanism of action of many classes of antibacterial agents has helped develop generalizations about the *in vitro* activity of a number of antimicrobial classes (table 1) [6–15]. For example, antibacterial drugs that disrupt the cell wall or cell membrane (i.e., cell wall–active drugs) or that interfere with essential bacterial enzymes are more likely to be bactericidal, compared with antibacterial drugs that inhibit protein synthesis.

In certain diseases (e.g., endocarditis), both animal models and clinical experience favor bactericidal agents [16–25]. Other studies suggest that combinations of bactericidal and bacteriostatic agents may lead to improved clinical outcomes, compared with either type of agent alone [23, 26, 27]. In the treatment of meningitis, however, studies show that the addition of a bacteriostatic agent dramatically worsened the outcome [28, 29]. The use of multiple agents adds another level of complexity, because both the mechanisms of action and the pharmacokinetics of the combined agents may influence whether their effects are synergistic, additive, or antagonistic when administered concomitantly. The specific infecting organism will also have an influence, because a given antibacterial agent may be bactericidal to one organism but bacteriostatic to another. *In vitro* studies indicate that, similar to eukaryotes, bacteria may

be activated to undergo programmed cell death (analogous to apoptosis in animal cells). One of the major initiators of programmed cell death is exposure to antibacterial agents, such as rifampin, chloramphenicol, and spectinomycin [30]. Chloramphenicol, for example, is bacteriostatic against most enteric gram-negative bacteria, but is also bactericidal against *Haemophilus influenzae* and *Streptococcus pneumoniae* at clinically achievable levels [31].

It is not necessarily possible to predict whether an antibacterial agent will have bactericidal activity for a given organism, because strain-to-strain variations may occur. Recent studies on the use of antibacterial agents suggest that the activity of antibacterial drugs can be classified as either concentration dependent or concentration independent (i.e., time dependent) [32]. Antibacterial agents that exhibit concentration-dependent killing cause rapid and extensive bactericidal activity. Such concentration-dependent agents include aminoglycosides and fluoroquinolones [32]. At optimal doses, the most rapid and extensive bacterial killing is achieved by aminoglycosides, fluoroquinolones, daptomycin (a new lipopeptide antibiotic), and oritavancin (an investigational glycopeptide), followed by some β -lactams [33–36]. The efficiency of killing for concentration-dependent agents is correlated with the peak serum concentration and MIC for the organism. The ratio of peak concentration to MIC for such agents is usually predictive of bacterial eradication [36–38].

With concentration-independent antibacterial drugs (these include some β -lactams, clindamycin, vancomycin, and linezolid [oxazolidinones]), the efficacy of the agent in eliminating microorganisms is dependent on the time that the serum drug level exceeds the MIC for the organism [32]. Increasing the serum concentration of the antibacterial agent may not lead to increased activity beyond a certain level. Therefore, administering antibacterial drugs with long half-lives or frequent dosing of antibacterial drugs with short half-lives is critical for successful treatment of an infection.

However, a cell wall–active antibacterial agent such as vancomycin, which kills slowly, may be inferior to a drug that works by inhibiting protein synthesis or transcription. The commonly held belief that cell wall–active antibacterial agents are always superior to drugs that work by inhibiting protein synthesis because the former are bactericidal and the latter are bacteriostatic is a potentially misleading oversimplification.

CNS INFECTIONS

A frequently cited study of *S. pneumoniae* meningitis showed that patients treated with penicillin monotherapy had a 21% mortality rate, compared with 79% in patients treated with penicillin plus chlortetracycline [28]. Penicillin alone is bactericidal, whereas the combination of penicillin plus chlortetracycline may not be. Thus, administration of the com-

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

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

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 chlortetracycline 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 streptococcus 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

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 $\leq 1:8$ was associated with failure of therapy in 83% of patients, whereas

a peak serum bactericidal titer of $\geq 1:16$ was associated with clinical success in 87% of patients. In patients with adequate neutrophil counts, a peak serum bactericidal titer of $\geq 1:8$ 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 *S. aureus* bacteremic pneumonia in which the mortality rate was 47% in patients treated with vancomycin, compared with 0% in patients treated with cloxacillin. 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 bacteriocidal 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 *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 *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 organisms are 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 β -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 *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.

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References

1. M21-A methodology for the serum bactericidal test, approved guideline. In: Program and abstracts of the National Committee Clinical Laboratory Standards (Wayne, Pennsylvania). 1999.
2. Wolfson JS, Swartz MN. Drug therapy: serum bactericidal activity as a monitor of antibiotic therapy. *N Engl J Med* 1985; 312:968–75.
3. Reller LB. The serum bactericidal test. *Rev Infect Dis* 1986; 8:803–8.
4. Stratton CW. Serum bactericidal test. *Clin Microbiol Rev* 1988; 1:19–26.
5. DeGirolami PC, Eliopoulos G. Antimicrobial susceptibility tests and their role in therapeutic drug monitoring. *Clin Lab Med* 1987; 7: 499–512.
6. Levison ME. Pharmacodynamics of antimicrobial agents: bactericidal and postantibiotic effects. *Infect Dis Clin North Am* 1995; 9:483–95.
7. Tally FP, DeBruin MF. Development of daptomycin for gram-positive infections. *J Antimicrob Chemother* 2000; 46:523–6.
8. Hancock R. Cationic peptides: effectors in innate immunity and novel antimicrobials. *Lancet Infect Dis* 2001; 1:156–64.

9. Brisson-Noel A, Trieu-Cuot P, Courvalin P. Mechanism of action of spiramycin and other macrolides. *J Antimicrob Chemother* **1988**; 22(Suppl B):13–23.
10. Hooper DC. Mechanisms of action of antimicrobials: focus on fluoroquinolones. *Clin Infect Dis* **2001**; 32(Suppl 1):S9–S15.
11. Quinlivan EP, McPartlin J, Weir DG, Scott J. Mechanism of the antimicrobial drug trimethoprim revisited. *FASEB J* **2000**; 14:2519–24.
12. Smilack JD. The tetracyclines. *Mayo Clin Proc* **1999**; 74:727–9.
13. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet* **2001**; 40:327–41.
14. Diekema DJ, Jones RN. Oxazolidinone antibiotics. *Lancet* **2001**; 358:1975–82.
15. Buchanan LV, Dailey CF, LeMay RJ, Zielinski RJ, Kuo MS, Gibson JK. Time-dependent antibacterial effects of linezolid in experimental rabbit endocarditis. *J Antimicrob Chemother* **2002**; 50:440–2.
16. Hunter TH. Speculations on the mechanism of cure of bacterial endocarditis. *J Am Med Assoc* **1950**; 144:524–7.
17. Archer G, Fekety FR Jr. Experimental endocarditis due to *Pseudomonas aeruginosa*. II. Therapy with carbenicillin and gentamicin. *J Infect Dis* **1977**; 136:327–35.
18. Carrizosa J, Kaye D. Antibiotic concentrations in serum, serum bactericidal activity, and results of therapy of streptococcal endocarditis in rabbits. *Antimicrob Agents Chemother* **1977**; 12:479–83.
19. Tight RR. Ampicillin therapy of experimental enterococcal endocarditis. *Antimicrob Agents Chemother* **1980**; 18:307–10.
20. Coleman DL, Horwitz RI, Andriole VT. Association between serum inhibitory and bactericidal concentrations and therapeutic outcome in bacterial endocarditis. *Am J Med* **1982**; 73:260–7.
21. Weinstein MP, Stratton CW, Ackley A, et al. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. *Am J Med* **1985**; 78:262–9.
22. Biró L, Iván E. Study of bactericidal and bacteriostatic antibiotics in animals with normal and suppressed immunity. *Chemotherapy* **1968**; 13:100–7.
23. Klastersky J. Concept of empiric therapy with antibiotic combinations: indications and limits. *Am J Med* **1986**; 80:2–12.
24. Chowdhury MH, Tunkel AR. Antibacterial agents in infections of the central nervous system. *Infect Dis Clin North Am* **2000**; 14:391–408, ix.
25. Weinstein MP, Stratton CW, Hawley HB, Ackley A, Reller LB. Multicenter collaborative evaluation of a standardized serum bactericidal test as a predictor of therapeutic efficacy in acute and chronic osteomyelitis. *Am J Med* **1987**; 83:218–22.
26. Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for Gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents* **1999**; 11:7–12.
27. Eliopoulos GM. Synergism and antagonism. *Infect Dis Clin North Am* **1989**; 3:399–406.
28. Lepper MH, Dowling HF. Treatment of pneumococcal meningitis with penicillin compared with penicillin plus aureomycin. *AMA Arch Intern Med* **1951**; 88:489–94.
29. Mathies AW Jr, Leedom JM, Ivler D, Wehrle PF, Portnoy B. Antibiotic antagonism in bacterial meningitis. *Antimicrobial Agents Chemother* **1967**; 7:218–24.
30. Engelberg-Kulka H, Sat B, Hazan R. Bacterial programmed cell death and antibiotics. *ASM News* **2001**; 67:617–24.
31. Feder HM Jr. Chloramphenicol: what we have learned in the last decade. *South Med J* **1986**; 79:1129–34.
32. Levison ME. Pharmacodynamics of antibacterial drugs. *Infect Dis Clin North Am* **2000**; 14:281–91, vii.
33. Lortholary O, Tod M, Cohen Y, Petitjean O. Aminoglycosides. *Med Clin North Am* **1995**; 79:761–87.
34. Akins RL, Rybak MJ. Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus* isolates in an in vitro pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother* **2001**; 45:454–9.
35. Harland S, Tebbs SE, Elliott TS. Evaluation of the in vitro activity of the glycopeptide antibiotic LY333328 in comparison with vancomycin and teicoplanin. *J Antimicrob Chemother* **1998**; 41:273–6.
36. Schentag JJ. Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUC to improve efficacy and avoid resistance. *J Chemother* **1999**; 11:426–39.
37. MacGowan AP. Role of pharmacokinetics and pharmacodynamics: does the dose matter? *Clin Infect Dis* **2001**; 33(Suppl 3):S238–9.
38. Gunderson BW, Ross GH, Ibrahim KH, Rotschafer JC. What do we really know about antibiotic pharmacodynamics? *Pharmacotherapy* **2001**; 21:302S–18S.
39. Scheld WM, Fletcher DD, Fink FN, Sande MA. Response to therapy in an experimental rabbit model of meningitis due to *Listeria monocytogenes*. *J Infect Dis* **1979**; 140:287–94.
40. Parkas V, Armstrong D. *Listeria monocytogenes*. In: Yu VL, Merigan TC, Barriere SL, eds. *Antimicrobial therapy and vaccines*. Baltimore: Williams & Wilkins, **1999**:278–9.
41. Jacobs RF. Cefotaxime treatment of gram-negative enteric meningitis in infants and children. *Drugs* **1988**; 35(Suppl 2):185–9.
42. McCracken GH Jr, Mize SG. A controlled study of intrathecal antibiotic therapy in gram-negative enteric meningitis of infancy: report of the neonatal meningitis cooperative study group. *J Pediatr* **1976**; 89:66–72.
43. Eng RH, Cherubin C, Smith SM, Buccini F. Examination of gram-negative bacilli from meningitis patients who failed or relapsed on moxalactam therapy. *Antimicrob Agents Chemother* **1984**; 26:850–6.
44. Galbreath, Hull. Sulfonamide therapy of bacterial endocarditis: results in 42 cases. *Ann Intern Med* **1943**; 18:201–3.
45. Christie RV. Penicillin in subacute bacterial endocarditis. *Br Med J* **1948**; 1:1–4.
46. Christie RV. Penicillin subacute bacterial endocarditis. *Br Med J* **1949**; 2:950–1.
47. Herzstein J, Ryan JL, Mangi RJ, Greco TP, Andriole VT. Optimal therapy for enterococcal endocarditis. *Am J Med* **1984**; 76:186–91.
48. Mandell GL, Kaye D, Levison ME, Hook EW. Enterococcal endocarditis: an analysis of 38 patients observed at the New York Hospital-Cornell Medical Center. *Arch Intern Med* **1970**; 125:258–64.
49. Jawetz E, Gunnison JB, Coleman VR. The combined action of penicillin with streptomycin or chloromycetin on enterococci in vitro. *Science* **1950**; 111:254–6.
50. Weinstein AJ, Moellering RC Jr. Penicillin and gentamicin therapy for enterococcal infections. *JAMA* **1973**; 223:1030–2.
51. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* **2001**; 345:1318–30.
52. Norden CW. Experimental osteomyelitis. IV. Therapeutic trials with rifampin alone and in combination with gentamicin, sisomicin, and cephalothin. *J Infect Dis* **1975**; 132:493–9.
53. Norden CW, Shaffer M. Treatment of experimental chronic osteomyelitis due to *Staphylococcus aureus* with vancomycin and rifampin. *J Infect Dis* **1983**; 147:352–7.
54. Bodey GP, Middleman E, Umsawadi T, Rodriguez V. Infections in cancer patients: results with gentamicin sulfate therapy. *Cancer* **1972**; 29:1697–701.
55. Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med* **1971**; 284:1061–5.
56. Bodey GP. Synergy: should it determine antibiotic selection in neutropenic patients? *Arch Intern Med* **1985**; 145:1964–6.
57. Klastersky J, Hensgens C, Meunier-Carpentier F. Comparative effectiveness of combinations of amikacin with penicillin G and amikacin with carbenicillin in gram-negative septicemia: double-blind clinical trial. *J Infect Dis* **1976**; 134(Suppl):S433–40.
58. Sculier JP, Klastersky J. Significance of serum bactericidal activity in gram-negative bacillary bacteremia in patients with and without granulocytopenia. *Am J Med* **1984**; 76:429–35.
59. Aparicio J, Oltra A, Llorca C, et al. Randomised comparison of cef-

- tazidime and imipenem as initial monotherapy for febrile episodes in neutropenic cancer patients. *Eur J Cancer* **1996**;32A:1739–43.
60. Cometta A, Calandra T, Gaya H, et al. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto Infection Program. *Antimicrob Agents Chemother* **1996**;40:1108–15.
 61. Wade JC, Standiford HC, Drusano GL, et al. Potential of imipenem as single-agent empiric antibiotic therapy of febrile neutropenic patients with cancer. *Am J Med* **1985**;78:62–72.
 62. Morgan G, Duerden BI, Lilleyman JS. Ceftazidime as a single agent in the management of children with fever and neutropenia. *J Antimicrob Chemother* **1983**;12(Suppl A):347–51.
 63. Pizzo PA, Hathorn JW, Hiemenz J, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* **1986**;315:552–8.
 64. Meunier F, Zinner SH, Gaya H, et al. Prospective randomized evaluation of ciprofloxacin versus piperacillin plus amikacin for empiric antibiotic therapy of febrile granulocytopenic cancer patients with lymphomas and solid tumors. The European Organization for Research on Treatment of Cancer International Antimicrobial Therapy Cooperative Group. *Antimicrob Agents Chemother* **1991**;35:873–8.
 65. Gleckman RA. Trimethoprim-sulfamethoxazole vs. ampicillin in chronic urinary tract infections: a double-blind multicenter cooperative controlled study. *JAMA* **1975**;233:427–31.
 66. Iravani A, Richard GA. Single-dose ceftriaxone versus multiple-dose trimethoprim-sulfamethoxazole in the treatment of acute urinary tract infections. *Antimicrob Agents Chemother* **1985**;27:158–61.
 67. Bohme 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.
 68. Freifeld AG, Walsh T, Marshall D, et al. Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol* **1995**;13:165–76.
 69. Feld R, DePauw B, Berman S, Keating A, Ho W. Meropenem versus ceftazidime in the treatment of cancer patients with febrile neutropenia: a randomized, double-blind trial. *J Clin Oncol* **2000**;18:3690–8.
 70. Gonzalez C, Rubio M, Romero-Vivas J, Gonzalez M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis* **1999**;29:1171–7.
 71. Rubinstein E, Cammarata S, Oliphant T, Wunderink R. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis* **2001**;32:402–12.
 72. Raad I, Bompert F, Hachem R. Prospective, randomized dose-ranging open phase II pilot study of quinupristin/dalfopristin versus vancomycin in the treatment of catheter-related staphylococcal bacteremia. *Eur J Clin Microbiol Infect Dis* **1999**;18:199–202.
 73. Fagon J, Patrick H, Haas DW, et al. Treatment of gram-positive nosocomial pneumonia: prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial Pneumonia Group. *Am J Respir Crit Care Med* **2000**;161:753–62.
 74. Burke JF. The effective period of preventive antibiotic action in experimental incision and dermal lesions. *Surgery* **1961**;50:161–8.
 75. Geiman BJ, Smith AL. Dexamethasone and bacterial meningitis: a meta-analysis of randomized controlled trials. *West J Med* **1992**;157:27–31.
 76. Wald ER, Kaplan SL, Mason EO Jr, et al. Dexamethasone therapy for children with bacterial meningitis. Meningitis Study Group. *Pediatrics* **1995**;95:21–8.
 77. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J. Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group. *Lancet* **1993**;342:457–61.
 78. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* **2002**;347:1549–56.
 79. Coyle E, Cha R, Rybak M. Influence of linezolid (L), penicillin (P), and clindamycin (C), alone and in combination, on streptococcal pyrogenic exotoxin A (SPE A) release [abstract A-2197]. In: Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C.: ASM Press, **2001**:38.
 80. Prins JM, van Agtmael MA, Kuijper EJ, van Deventer SJ, Speelman P. Antibiotic-induced endotoxin release in patients with gram-negative urosepsis: a double-blind study comparing imipenem and ceftazidime. *J Infect Dis* **1995**;172:886–91.
 81. Tauber MD, Shibl AM, Hackbarth CJ, Larrick JW, Sande MA. Antibiotic therapy, endotoxin concentration in cerebrospinal fluid, and brain edema in experimental *Escherichia coli* meningitis in rabbits. *J Infect Dis* **1987**;156:456–62.
 82. Nau R, Eiffert H. Modulation of release of proinflammatory bacterial compounds by antibacterials: potential impact on course of inflammation and outcome in sepsis and meningitis. *Clin Microbiol Rev* **2002**;15:95–110.
 83. Molbak K, Mead PS, Griffin PM. Antimicrobial therapy in patients with *Escherichia coli* O157:H7 infection. *JAMA* **2002**;288:1014–6.