Clinical Infectious Diseases

INVITED ARTICLE

REVIEWS OF ANTI-INFECTIVE AGENTS: Louis Saravolatz, Section Editor

Busting the Myth of "Static vs Cidal": A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

[1]Los Angeles County + University of Southern California Medical Center and [2]Division of Infectious Diseases, Keck School of Medicine at the University of Southern California, Los Angeles

We sought to determine if clinical data validate the dogma that bactericidal antibiotics are more clinically effective than bacteriostatic agents. We performed a systematic literature review of published, randomized, controlled trials (RCTs) that compared a bacteriostatic agent to a bactericidal agent in the treatment of clinical, bacterial infections. Of 56 identified trials published since 1985, 49 found no significant difference in efficacy between bacteriostatic and bactericidal agents. In 6 trials it was found that the bacteriostatic agent was superior to the bactericidal agent in efficacy. Only 1 trial found that the bactericidal agent was superior; in that case, the inferiority of the static agent was explainable by underdosing of the drug based on pharmacokinetic–pharmacodynamic analysis. Thus, virtually all available data from high-quality, RCTs demonstrate no intrinsic superiority of bactericidal compared to bacteriostatic agents. Other drug characteristics such as optimal dosing, pharmacokinetics, and tissue penetration may be more important efficacy drivers.

Keywords. antibiotic; static; cidal; systematic literature review; efficacy.

Despite 80 years of experience, we are still learning how to optimally use antibiotics clinically. A common dogma in medicine is the belief that bactericidal agents are more effective than bacteriostatic agents. Common etymologic intuition might lead one to believe that a bacteriostatic antibiotic simply halts bacterial growth and that a bactericidal agent kills or eliminates bacteria. Conceptually, it might seem logical that we should preferentially prescribe the latter because they are believed to be better at killing bacteria.

Unfortunately, these pervasive beliefs about the meaning of bacteriostatic and bactericidal are misunderstood [1]. Bacteriostatic antibiotics do kill bacteria; they just require a higher concentration than bactericidal agents to achieve specific thresholds of bacterial reduction. Given that the definitions of bactericidal and bacteriostatic are based on convention rather than clinical principles, we sought to determine if clinical evidence exists to confirm or refute the concept that bactericidal antibiotics are more effective than bacteriostatic agents. To test this hypothesis, we performed a systematic review of published, randomized, controlled trials (RCTs) that compared clinical outcomes of bacteriostatic and bactericidal agents when treating invasive bacterial infections.

Received 8 October 2017; editorial decision 2 December 2017; accepted 22 December 2017; published online December 26, 2017.

Correspondence: B. Spellberg, LAC + USC Medical Center, 2051 Marengo Street, Los Angeles, CA 90033 (bspellberg@dhs.lacounty.gov).

Clinical Infectious Diseases® 2018;66(9):1470–4

© The Author(s) 2017. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cix1127

METHODS

We performed a comprehensive search of the medical literature to review the available data that compared bactericidal agents to bacteriostatic antibiotics in the treatment of clinical infections. The PubMed database was searched using the following terms for commonly used bacteriostatic agents: "azithromycin" OR "chloramphenicol" OR "clarithromycin" OR "clindamycin" OR "doxycycline" OR "linezolid" OR "erythromycin" OR "tetracycline" OR "tigecycline" OR "eravacycline." The terms were used in search combination with publication type: "randomized controlled trial." English language papers published between January 1985 and September 2017 were reviewed. RCTs that compared bacteriostatic agents to bactericidal agents were included in the review. Observational/retrospective studies were excluded. Trials were also excluded if they compared bacteriostatic to bacteriostatic or bactericidal to bactericidal agents.

RESULTS

Overall Findings

In our systematic literature review, we identified 56 RCTs that compared the clinical efficacy of bacteriostatic agents to that of bactericidal antibiotics head-to-head for patients with serious or life-threatening, invasive bacterial infections (Supplementary Table 1). Most (n = 49, 81%) of the trials found no significant difference in efficacy between bacteriostatic and bactericidal antibiotics, including for potentially highly lethal infections such as typhoid fever, bacteremia, plague, and pneumonia.

Six trials that did find a significant efficacy difference between bacteriostatic and bactericidal agents actually found that the bacteriostatic agent was more effective than the bactericidal agent (Supplementary Table 1). Only 1 trial found

Downloaded from https://academic.oup.com/cid/article-abstract/66/9/1470/4774989
by University of Durham user
on 23 April 2018

a bactericidal antibiotic to be superior in efficacy to a static agent; that trial compared tigecycline to imipenem for the treatment of ventilator-associated pneumonia and found that tigecycline was inferior [2]. However, pharmacologic analysis determined that the tigecycline dose used in the trial was too low, resulting in inadequate drug levels compared to the susceptibility of the bacteria that caused the infections [3]. When a subsequent trial was done with double the dose of tigecycline, tigecycline was similar in efficacy to imipenem for the same disease [4]. Subsequent trials in skin and soft tissue infections (SSTIs) [5–8], community-acquired pneumonia [9–12], and intraabdominal infections [13–16] showed equivalent clinical efficacy for tigecycline and several bactericidal comparators (Supplementary Table 1). A metaanalysis suggested worse outcomes with tigecycline compared to competitors [17]. However, the efficacy difference was driven largely by the trial for ventilator-associated pneumonia; the other trials that were included did not individually find a difference in efficacy between tigecycline and the comparator. Other authors have suggested that the metaanalysis must be interpreted with caution given its statistical methods [18] and dosing heterogeneity [19].

Skin and Soft Tissue Infections

We also evaluated the studies based on the site of the infection. We identified 19 trials that compared clinical outcomes of bacteriostatic agents to a bactericidal agent for the treatment of SSTIs. Three trials found statistically superior clinical outcomes with linezolid (bacteriostatic) compared to vancomycin (bactericidal) in the treatment of complicated SSTIs (Supplementary Table 1). Several additional trials found linezolid to be not significantly different in clinical efficacy compared to vancomycin across a range of nonendocarditis gram-positive infections (Supplementary Table 1). Linezolid was also shown in several of the same SSTI studies to have superior or noninferior microbiologic eradication rates compared to bacteriostatic agents (Supplementary Table 1). Even when treating methicillin-resistant *Staphylococcus aureus* (MRSA), the use of a bactericidal regimen (trimethoprim–sulfamethoxazole plus rifampicin) was shown to have outcomes equivalent to those for bacteriostatic linezolid across a variety of MRSA infections (Supplementary Table 1).

A particularly interesting study [20] was linezolid vs vancomycin in febrile neutropenic patients; it remains one of the only studies on this subject to include neutropenic hosts, a group of patients for which bactericidal therapy has traditionally been thought to be superior (Supplementary Table 1). The trial concluded that linezolid and vancomycin had similar efficacy in febrile neutropenic patients with cancer. Caution must be taken in the widespread application of this conclusion to all infections in immunocompromised hosts as no prospective studies that compared a bactericidal to a bacteriostatic agent active for gram-negative bacteria in the neutropenic population were identified. Furthermore, vancomycin dosing may not have been optimal, and add-on bactericidal therapy was permitted in this study. Nevertheless, this RCT did find that a bacteriostatic agent was not inherently inferior to a bactericidal one in infected neutropenic hosts.

Clinical outcomes for SSTIs have also been shown to be equivalent when linezolid was compared to newer bactericidal agents including dalbavancin and teicoplanin (Supplementary Table 1). Although the study that compared linezolid to teicoplanin showed no difference in clinical outcomes between teicoplanin for SSTIs or pneumonia, it did show statistically significant clinical superiority of linezolid over teicoplanin in the all-infections ($P = .005$) and bacteremia ($P = .009$) subgroup analyses (Supplementary Table 1).

Pneumonia

A total of 19 trials were identified that compared a bacteriostatic agent to a bactericidal agent for the treatment of pneumonia, and additional trials included pneumonia in specific subgroup analyses (Supplementary Table 1). Linezolid was studied for pneumonia in a variety of settings and found to have superior or similar clinical efficacy compared to vancomycin for both nosocomial and community-acquired pneumonia (Supplementary Table 1). These outcome differences may be due in part to the poor penetration of vancomycin in alveolar tissues, whereas linezolid penetrates these tissues very well [21–25]. Nevertheless, the finding of similar to superior efficacy of linezolid reinforces that static vs cidal in vitro killing does not intrinsically make the static agent inferior clinically; other drug characteristics are as or more important to clinical effect.

Similarly, clinically equivalent results were seen in a comparison of linezolid and teicoplanin (bactericidal) for nosocomial and critically ill patients with pneumonia (Supplementary Table 1). In the distinct setting of community-acquired pneumonia, including atypical pneumonia, the bacteriostatic agent doxycycline was shown to be clinically equivalent to β-lactam–based or fluoroquinolone-based (bactericidal) regimens (Supplementary Table 1). Clindamycin, which is bacteriostatic against culpable anaerobes, was shown in 2 trials of aspiration pneumonia to result in no difference in clinical outcomes compared to the bactericidal agents penicillin and ampicillin–sulbactam, as well as the carbapenem–β-lactamase inhibitor combination panipenem–betamipron (Supplementary Table 1).

As mentioned, the only trial in which a cidal agent (imipenem) was found to be superior in efficacy to a static agent (tigecycline) was a trial of ventilator-associated pneumonia [2]. However, a follow-up study of double-dose tigecycline found the 2 drugs to be similarly effective for the same disease [4]. Four other studies [9–12] found no difference in pneumonia outcomes of tigecycline vs levofloxacin.

Downloaded from https://academic.oup.com/cid/article-abstract/66/9/1470/4774989
by University of Durham user
on 23 April 2018

Typhoid Fever/Salmonellosis

Enteric fever due to *Salmonella typhi* has served as a unique bacterial entity for the clinical comparison of bacteriostatic and bactericidal agents. Five studies compared the bacteriostatic agent chloramphenicol to bactericidal β-lactams or fluoroquinolones for typhoid fever, and none showed statistically significant differences in clinical outcomes (Supplementary Table 1). Although chloramphenicol was associated with higher rates of hematologic toxicities, it was shown to have unique benefits including decreased levels of the proinflammatory cytokine interleukin-1β [26] compared to these other agents. Similar to chloramphenicol, the bacteriostatic macrolide azithromycin was compared to bactericidal β-lactams and fluoroquinolones with no statistically significant difference seen in clinical outcomes in patients with typhoid fever (Supplementary Table 1).

Other Infections

Other studies have shown equivalent clinical outcomes with the use of bacteriostatic and bactericidal agents in genital infections including chlamydia in women (azithromycin vs the bactericidal rifamycin, rifalazil) and bacterial vaginosis (clindamycin vs bactericidal metronidazole; Supplementary Table 1). In complicated intraabdominal infections, tigecycline and the novel fluorocycline eravacycline (bacteriostatic) were shown to be clinically equivalent to bactericidal comparators (Supplementary Table 1). Even in the treatment of plague, bacteriostatic doxycycline was found to be equivalent to the bactericidal aminoglycoside, gentamicin (Supplementary Table 1).

DISCUSSION

While it seems intuitive that antibiotics that more rapidly kill bacteria should be more clinically effective, a systematic review of RCTs does not support this assertion. Furthermore, there are a variety of misunderstandings around the meaning of the terms "bactericidal" and "bacteriostatic." When asked what bacteriostatic means, many providers will respond that bacteriostatic agents slow or inhibit the growth of bacteria but do not kill them, as compared to bactericidal antibiotics that actively kill. Although that interpretation is what the names seem to imply, the interpretation is wrong.

Two definitions are important to clarify. First, the minimum inhibitory concentration (MIC) is defined as the concentration that inhibits visible bacterial growth at 24 hours of growth in specific media, at a specific temperature, and at a specific carbon dioxide concentration. Second, the minimum bactericidal concentration (MBC) is the concentration of a drug that results in a 1000-fold reduction in bacterial density at 24 hours of growth in the same specific conditions. The formal definition of a bactericidal antibiotic is one for which the ratio of MBC-to-MIC is ≤4, while a bacteriostatic agent has an MBC-to-MIC ratio of >4 [1].

Thus, an antibiotic that achieves a >1000-fold reduction in bacterial density but does so at a concentration that is 8-fold above the MIC of the drug is considered to be bacteriostatic, despite the fact that it clearly kills the bacteria. Similarly, an antibiotic that achieves a 10-fold, or even a 500-fold, reduction in bacterial density at a concentration of 2- to 4-fold above the MIC is characterized as bacteriostatic, even though it demonstrates impressive killing ability. All antibiotics that are considered bacteriostatic do kill bacteria in vitro, just at concentrations that are farther above their MICs than bactericidal agents.

Furthermore, these purely laboratory definitions are somewhat arbitrary. Why should it be that the MBC requires a 1000-fold reduction in bacterial density as opposed to 100-, 500-, 5000-, or even a 10 000-fold reduction? Why 24 hours? Why must the MBC not be more than 4-fold above the MIC as opposed to only 2-fold or for that matter 16-fold or 24-fold? Ultimately, it is reasonable to standardize in vitro comparisons of rapidity of kill by antimicrobial agents if there is believed to be some value in knowing this characteristic of an agent. However, that does not mean that this current standardized method is predictive of what happens during a clinical infection. Bacteriostatic and bactericidal are relative in vitro terms not based on linkage to any predictive ability of the outcome of infections in vivo.

Our analysis of published RCTs demonstrates that bactericidal agents are not intrinsically superior in efficacy to bacteriostatic agents. The majority of trials across a variety of infections found no difference in efficacy between bacteriostatic and bactericidal agents. Of 7 trials that did find a statistically significant difference in clinical outcomes, 6 found that the bacteriostatic agent was superior in efficacy. The only trial that found the bactericidal agent to be superior in efficacy used a pharmacologically suboptimal dose of the static agent, such that a repeat trial using double the dose of the static agent found no difference in efficacy between the static and cidal agents. Thus, RCTs do not support the superiority of bactericidal agents. Rather, the available data suggest that other drug characteristics such as optimal dosing, pharmacokinetics, and tissue penetration may be more important drivers of clinical efficacy than intrinsic rate of bacterial killing in vitro.

The origin of the bacteriostatic vs bactericidal debate appears to derive from older case series that evaluated patients with bacterial endocarditis. In the 1950s, Finland found that bacteriostatic agents, including a variety of tetracyclines and macrolides, resulted in poor outcomes when used to treat endocarditis [27, 28]. These studies led to the belief that bacteriostatic agents generally are inferior as therapeutic agents for endocarditis. Indeed, it is widely accepted that the cardiac valves are relatively immunosuppressed regions given poor accessibility to phagocytic cells. Therefore, from a pathophysiologic standpoint, phagocyte-independent killing by bactericidal antibiotics is considered preferable for endocarditis. However, as mentioned, bacteriostatic antibiotics do kill bacteria, but the bacteriostatic agents in these older series (tetracyclines and

Downloaded from https://academic.oup.com/cid/article-abstract/66/9/1470/4774989
by University of Durham user
on 23 April 2018

macrolides) achieve very low blood concentrations. Thus, based only on pharmacological principles unrelated to their rapidity of microbial killing, such agents would not be anticipated to be desirable for the treatment of bloodstream infections.

In contrast to the older bacteriostatic agents, the bacteriostatic agent linezolid has more favorable bloodstream pharmacokinetics. Linezolid has been found in a few published case series to result in relatively good outcomes when used for bacterial endocarditis [29–31]. Although not inclusive of bacterial endocarditis, several of the trials included in this review included bacteremia in either primary or subgroup analyses of linezolid vs a comparator bactericidal agent. In direct comparison to the bactericidal drugs vancomycin and teicoplanin, linezolid was also shown to have superior or no relevant difference in clinical outcomes for gram-positive bloodstream infections (Supplemental Table 1). In one trial [32] (included in this review with equivalent clinical outcomes for SSTIs), linezolid-attributed mortality was higher only among patients with gram-negative bacteremia. Since linezolid is not normally used to treat gram-negative bacteria, it is not entirely clear how to interpret this finding. One possible interpretation, based on a single in vitro pharmacodynamic model [33], is that linezolid may attenuate the activity of agents active against gram-negative organisms.

Clinical support for bactericidal therapy in meningitis, another immune privileged site of infection, comes from older, nonrandomized, observational studies of pneumococcal meningitis in the 1950s in which penicillin monotherapy showed lower mortality than penicillin combined with a bacteriostatic tetracycline [34, 35]. However, other more recent experimental animal models of infections, including post-viral bacterial pneumonia [36, 37] and sinusitis [38], have shown a survival advantage of a protein synthesis–inhibiting bacteriostatic agent compared to comparator bactericidal agents. These beneficial effects may be due to reduction in inflammatory immunopathology that occurs during treatment, but again, these studies do not include the generally accepted bactericidal-warranting conditions of endocarditis or meningitis.

Our study has a number of limitations. Although RCTs are the "gold-standard" for clinical research because they are substantially less likely to be affected by numerous types of bias, they often exclude patients with more severe or life-threatening infections or hosts with impaired immunity from enrollment. Retrospective comparative trials permit analysis of patients with more severe outcomes. However, as such studies are subject to numerous types of bias, they are typically viewed as hypothesis generating, with findings that require confirmation in a RCT. Thus, we did not analyze observational or retrospective studies.

Additionally, the quality of the trials we included was mixed. The majority (32 of 56) were nonblinded, leading to risk of performance bias. However, the studies that were blinded reached the same conclusions as the nonblinded studies; indeed, only 1 of 56 studies found a cidal agent to be superior in efficacy to a static agent. Hence, there was concordance of conclusions across virtually all the studies. Our findings are similar to those from a previous metaanalysis on this topic [39]. That analysis of partially overlapping trials identified possible selection, performance, attrition, and reporting biases in a number of the studies that were analyzed in both their study and in ours. However, given the robustness of the findings, the authors of that metaanalysis still concluded that the categorization of antibiotics into bacteriostatic and bactericidal likely has little clinical relevance. Finally, we were not able to identify trials that compared static agents to cidal agents for the treatment of bacterial endocarditis or bacterial meningitis. For these diseases, no conclusions can be definitively drawn from an analysis of RCTs.

In summary, there is extensive evidence that bactericidal and bacteriostatic agents are similar in efficacy when used to treat clinical infections, including SSTIs, pneumonia, nonendocarditis bloodstream infections, intraabdominal infections, and genital infections. The large majority of studies that compared bacteriostatic and bactericidal agents head-to-head for the treatment of invasive bacterial infections found no differences in clinical outcomes or mortality. When differences were found in such studies, the bacteriostatic agent was usually found to be superior and more cost-effective than the bactericidal agent. When bacteriostatic agents were found to be inferior, the explanation appears to be more likely inadequate dosing and/or achievable levels at the site of infection, not rapidity of kill of the microbe. It is time to abandon the notion that bactericidal antibiotic agents are intrinsically more effective than bacteriostatic agents.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (grants R01 AI130060, R01 HSO25690, R01 AI1081719, and R21 AI127954).

Potential conflict of interest. B. S. has consulted for Cempra, the Medicines Company, Medimmune, Tetraphase, AstraZeneca, Merck, Genentech, Forge, and Pfizer and owns equity in BioAIM, Synthetic Biologics, and Mycomed. The remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. Clin Infect Dis **2004**; 38:864–70.
2. Freire AT, Melnyk V, Kim MJ, et al; 311 Study Group. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis **2010**; 68:140–51.
3. Bhavnani SM, Rubino CM, Hammel JP, et al. Pharmacological and patient-specific response determinants in patients with hospital-acquired pneumonia treated with tigecycline. Antimicrob Agents Chemother **2012**; 56:1065–72.

Downloaded from https://academic.oup.com/cid/article-abstract/66/9/1470/4774989
by University of Durham user
on 23 April 2018

4. Ramirez J, Dartois N, Gandjini H, Yan JL, Korth-Bradley J, McGovern PC. Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. Antimicrob Agents Chemother **2013**; 57:1756–62.
5. Breedt J, Teras J, Gardovskis J, et al; Tigecycline 305 cSSSI Study Group. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. Antimicrob Agents Chemother **2005**; 49:4658–66.
6. Chuang YC, Chang CM, Aradhya S, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. J Microbiol Immunol Infect **2011**; 44:116–24.
7. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E; Tigecycline 300 cSSSI Study Group; Tigecycline 305 cSSSI Study Group. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis **2005**; 41 Suppl 5:S341–53.
8. Sacchidanand S, Penn RL, Embil JM, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: results from a phase 3, randomized, double-blind trial. Int J Infect Dis **2005**; 9:251–61.
9. Bergallo C, Jasovich A, Teglia O, et al; 308 Study Group. Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin. Diagn Microbiol Infect Dis **2009**; 63:52–61.
10. Dartois N, Castaing N, Gandjini H, Cooper A; Tigecycline 313 Study Group. Tigecycline versus levofloxacin for the treatment of community-acquired pneumonia: European experience. J Chemother **2008**; 20(Suppl 1):28–35.
11. Tanaseanu C, Bergallo C, Teglia O, et al; 308 Study Group; 313 Study Group. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. Diagn Microbiol Infect Dis **2008**; 61:329–38.
12. Tanaseanu C, Milutinovic S, Calistru PI, et al; 313 Study Group. Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC Pulm Med **2009**; 9:44.
13. Chen Z, Wu J, Zhang Y, et al. Efficacy and safety of tigecycline monotherapy vs. imipenem/cilastatin in Chinese patients with complicated intra-abdominal infections: a randomized controlled trial. BMC Infect Dis **2010**; 10:217.
14. Oliva ME, Rekha A, Yellin A, et al. A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [Study ID Numbers: 3074A1-301-WW; ClinicalTrials.gov Identifier: NCT00081744]. BMC Infect Dis **2005**; 5:88.
15. Qvist N, Warren B, Leister-Tebbe H, et al. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. Surg Infect (Larchmt) **2012**; 13:102–9.
16. Towfigh S, Pasternak J, Poirier A, Leister H, Babinchak T. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. Clin Microbiol Infect **2010**; 16:1274–81.
17. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother **2011**; 66:1963–71.
18. Curcio D, Verde PE. Comment on: efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother **2011**; 66:2893–5; author reply 5–6.
19. Scaglione F. Comment on: efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother **2011**; 66:2892–3; author reply 5–6.
20. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis **2006**; 42:597–607.
21. Conte JE Jr, Golden JA, Kipps J, Zurlinden E. Intrapulmonary pharmacokinetics of linezolid. Antimicrob Agents Chemother **2002**; 46:1475–80.
22. Boselli E, Breilh D, Rimmelé T, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. Crit Care Med **2005**; 33:1529–33.
23. Boselli E, Breilh D, Caillault-Sergent A, et al. Alveolar diffusion and pharmacokinetics of linezolid administered in continuous infusion to critically ill patients with ventilator-associated pneumonia. J Antimicrob Chemother **2012**; 67:1207–10.
24. Lamer C, de Beco V, Soler P, et al. Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. Antimicrob Agents Chemother **1993**; 37:281–6.
25. Lodise TP, Drusano GL, Butterfield JM, Scoville J, Gotfried M, Rodvold KA. Penetration of vancomycin into epithelial lining fluid in healthy volunteers. Antimicrob Agents Chemother **2011**; 55:5507–11.
26. Gasem MH, Keuter M, Dolmans WM, Van Der Ven-Jongekrijg J, Djokomoeljanto R, Van Der Meer JW. Persistence of Salmonellae in blood and bone marrow: randomized controlled trial comparing ciprofloxacin and chloramphenicol treatments against enteric fever. Antimicrob Agents Chemother **2003**; 47:1727–31.
27. Finland M. Current status of therapy in bacterial endocarditis. J Am Med Assoc **1958**; 166:364–73.
28. Finland M. Treatment of bacterial endocarditis. N Engl J Med **1954**; 250:372–83; contd.
29. Mancino P, Ucciferri C, Falasca K, Pizzigallo E, Vecchiet J. Methicillin-resistant *Staphylococcus epidermidis* (MRSE) endocarditis treated with linezolid. Scand J Infect Dis **2008**; 40:67–73.
30. Tascini C, Bongiorni MG, Doria R, et al. Linezolid for endocarditis: a case series of 14 patients. J Antimicrob Chemother **2011**; 66:679–82.
31. Lauridsen TK, Bruun LE, Rasmussen RV, et al. Linezolid as rescue treatment for left-sided infective endocarditis: an observational, retrospective, multicenter study. Eur J Clin Microbiol Infect Dis **2012**; 31:2567–74.
32. Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. Clin Infect Dis **2009**; 48:203–12.
33. LaPlante KL, Sakoulas G. Evaluating aztreonam and ceftazidime pharmacodynamics with *Escherichia coli* in combination with daptomycin, linezolid, or vancomycin in an in vitro pharmacodynamic model. Antimicrob Agents Chemother **2009**; 53:4549–55.
34. Lepper MH, Dowling HF. Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin; studies including observations on an apparent antagonism between penicillin and aureomycin. AMA Arch Intern Med **1951**; 88:489–94.
35. Olsson RA, Kirby JC, Romansky MJ. Pneumococcal meningitis in the adult. Clinical, therapeutic, and prognostic aspects in forty-three patients. Ann Intern Med **1961**; 55:545–9.
36. Karlström A, Boyd KL, English BK, McCullers JA. Treatment with protein synthesis inhibitors improves outcomes of secondary bacterial pneumonia after influenza. J Infect Dis **2009**; 199:311–9.
37. Karlström A, Heston SM, Boyd KL, Tuomanen EI, McCullers JA. Toll-like receptor 2 mediates fatal immunopathology in mice during treatment of secondary pneumococcal pneumonia following influenza. J Infect Dis **2011**; 204:1358–66.
38. Luxameechanporn T, Blair C, Kirtsreesakul V, Thompson K, Naclerio RM. The effect of treatment with moxifloxacin or azithromycin on acute bacterial rhinosinusitis in mice. Int J Infect Dis **2006**; 10:401–6.
39. Nemeth J, Oesch G, Kuster SP. Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis. J Antimicrob Chemother **2015**; 70:382–95.

Downloaded from https://academic.oup.com/cid/article-abstract/66/9/1470/4774989
by University of Durham user
on 23 April 2018