

# The Case for Accelerated Susceptibility Testing in the Era of Antibiotic Resistance

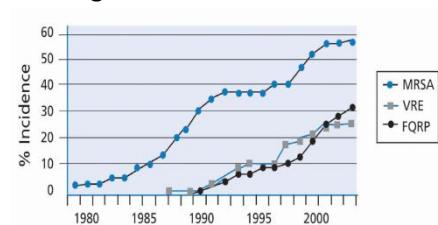
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Historically, infectious diseases have been a primary cause of mortality. With the advent of safe and effective antibiotics in the middle of the 20<sup>th</sup> century, deaths from bacterial infectious diseases became relatively rare and were no longer considered a pressing medical problem. A generation ago, many doctors believed that antibiotics had allowed humanity to declare victory in the war against bacterial diseases. Even as recently as 1986, a leading physician and medical educator could declare that "... I cannot conceive the need for more infectious disease experts."<sup>1</sup>

This golden age of antibiotics has ended and is unlikely to return. In the golden age, nearly all bacteria were susceptible to most antibiotics, and physicians could be confident in the efficacy of standard antibiotic therapy protocols. Although resistance to first-generation drugs such as penicillin emerged, these drugs could be replaced by the new discoveries that were regularly emerging from the pharmaceutical industry.

Rising Antibiotic Resistance



Sources: Centers for Disease Control and Prevention and the Infectious Disease Society of America

Now, all the low-hanging fruit in antibiotic discovery has been picked clean. New antibiotics are rare and in most instances, offer little to nothing over older antibiotics. Many are so similar to existing agents that resistance emerges within a few years of introduction.

Despite these trends, the management of infectious diseases is little changed. Most antibiotic therapy is empiric, i.e. physicians select antibacterials with little to no data to guide their choice. Lacking specific data on resistance and susceptibility, the standard course is to place patients on broad-spectrum agents that have wide but limited efficacy. One of the reasons for this course is that it can take 2-3 days for the receipt of laboratory results that allow optimization of therapy. Consequently, "inappropriate" (unnecessarily broad spectrum) therapy can continue for long time periods, increasing antibacterial resistance selection pressure. Similarly, the rise in methicillin-resistant *S. aureus* infection has resulted in the opposite problem, i.e. patients often are not adequately covered for this pathogen. Patients with deadly *S. aureus* bloodstream infections, which have mortality rates of greater than 30%, receive appropriate antibiotics in only half of all cases<sup>2</sup>. The current state of empirical antibacterial treatment for *S. aureus* has deteriorated to the point that it has been compared to a coin toss<sup>3</sup>.

<sup>1</sup> Petersdorf. Whither infectious diseases? Memories, manpower, and money. *J Infect Dis* (1986) vol. 153 (2) pp. 189-95

<sup>2</sup> Kaye et al. The deadly toll of invasive methicillin-resistant *Staphylococcus aureus* infection in community hospitals. *Clin Infect Dis* (2008) vol. 46 (10) pp. 1568-77

<sup>3</sup> Herzke et al. Empirical antimicrobial therapy for bloodstream infection due to methicillin-resistant *Staphylococcus aureus*: no better than a coin toss. *Infect Control Hosp Epidemiol* (2009) vol. 30 (11) pp. 1057-61

The impact of antibiotic resistance on mortality and associated treatment costs is significant. Hospital-acquired bacterial infections now exceed 1.7M per year in the US, resulting in over 100K deaths<sup>4</sup>. Antibiotic resistance is considered a contributing factor in 75% or more of these deaths<sup>5</sup>. Considering that these data do not include community-acquired infections (principally pneumonia), it is likely that the number of Americans killed by antibiotic resistant bacteria each year exceeds 100,000. This number exceeds the deaths from breast cancer, prostate cancer and AIDS combined<sup>6</sup>.

Although resistance to one or more antibiotics is widespread, nearly all bacteria are susceptible to at least one antibiotic. The challenge is identifying the appropriate antibiotic in a rapid, efficient manner. Current susceptibility testing methods require 2-4 days to return a result. Rapid antibiotic susceptibility testing has the potential to improve the treatment of infectious disease, reduce mortality, length of stay, and provider costs.

### **Case Study: Value of Accelerated Antibiotic Susceptibility Knowledge**

400 bed metropolitan hospital in the Midwest, U.S.



*A patient presenting with suspected endocarditis is hospitalized and vancomycin is empirically prescribed. Prior to receipt of antibacterial therapy, blood cultures were drawn and sent to the microbiology laboratory. In light of the current hospital susceptibility patterns (68% rate of MRSA), vancomycin is an appropriate empirical choice*

*After three days of vancomycin therapy, the patient's condition steadily worsened, with infection spreading to her spinal column and bones. The blood culture was positive within 12 hours (relatively early) and the Gram stain showed cocci in clusters, indicating Staphylococcus spp. The patient was continued on vancomycin and a standard broth dilution culture and susceptibility test was initiated. Forty eight (48) hours later, the pathogen was identified as methicillin- susceptible Staph aureus (MSSA). Based upon this information, the patient was immediately switched from vancomycin to nafcillin. The change in therapy was associated with rapid response to the nafcillin with associated resolution of symptoms.*

*The attending physician presented this case at grand rounds. Had results confirming MSSA been available earlier, he would have changed therapy to nafcillin earlier. Nafcillin is associated with more rapid clinical response than vancomycin and more rapid initiation of this agent might have resulted in more rapid recovery and fewer complications.*

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<sup>4</sup> Klevens et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep (2007) vol. 122 (2) pp. 160-6

<sup>5</sup> Klevens et al. The impact of antimicrobial-resistant, health care-associated infections on mortality in the United States. Clin Infect Dis (2008) vol. 47 (7) pp. 927-30

<sup>6</sup> Prostate cancer: 32,050 deaths in 2010, <http://www.seer.cancer.gov/statfacts/html/prost.html>. Breast cancer: 39,840 deaths in 2010, <http://www.seer.cancer.gov/statfacts/html/breast.html>. HIV/AIDS: 11,295 deaths in 2007, <http://www.cdc.gov/nchs/fastats/aids-hiv.htm>

This case illustrates several important points. First, in light of the fact that 68% of the *S. aureus* strains at his hospital were methicillin-resistant, vancomycin was an appropriate initial empirical choice. Second, this is an example of current treatment standards yielding a poorer outcome. Vancomycin is the default choice for treatment of Staph infections because resistance to it is still rare. However, it is not always the best choice: compared to other antibiotics, it has less favorable tissue perfusion characteristics<sup>7,8,9</sup> it does not kill bacteria as effectively<sup>10</sup>, appropriate dosing is challenging, it often requires a central line and therapeutic monitoring, and it has a significant toxicity profile<sup>11,12,13</sup>. In addition, the incidence of low level vancomycin resistance is increasing, which is associated with clinical failure and which threatens the long-term utility of the drug. Third, the doctor, knowing the limitations of vancomycin therapy, switched to a more-effective drug as soon as he knew that the infection would respond to it. However, he had to wait 2 additional days for this information. Fourth, this delay had a devastating effect on the patient. Hours count.

### Accelerating Antibiotic Susceptibility Testing Results

Timely and accurate detection and reporting of bloodstream infection are critical functions of a clinical microbiology laboratory. Antimicrobial susceptibility test (AST) results can affect both the clinician's choice of antimicrobial therapy and patient outcome<sup>14</sup>. Prompt detection of bloodstream infection, pathogen identification and antibiotic susceptibility are critical to ensure the best patient outcomes<sup>15, 16</sup>.



<sup>7</sup> Lamer et al. Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. *Antimicrob Agents Chemother* (1993) vol. 37 (2) pp. 281-6

<sup>8</sup> Stein and Wells. The importance of tissue penetration in achieving successful antimicrobial treatment of nosocomial pneumonia and complicated skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*: vancomycin and linezolid. *Curr Med Res Opin* (2010) vol. 26 (3) pp. 571-88

<sup>9</sup> Estes and Derendorf. Comparison of the pharmacokinetic properties of vancomycin, linezolid, tigecyclin, and daptomycin. *Eur J Med Res* (2010) vol. 15 (12) pp. 533-43

<sup>10</sup> Small and Chambers. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. *Antimicrob Agents Chemother* (1990) vol. 34 (6) pp. 1227-31

<sup>11</sup> Stevens. The role of vancomycin in the treatment paradigm. *Clin Infect Dis* (2006) vol. 42 Suppl 1 pp. S51-7

<sup>12</sup> Wong-Beringer et al. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. *Int J Antimicrob Agents* (2011) vol. 37 (2) pp. 95-101

<sup>13</sup> Pritchard et al. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. *Am J Med* (2010) vol. 123 (12) pp. 1143-9

<sup>14</sup> Tan et al. Laboratory antibiotic susceptibility reporting and antibiotic prescribing in general practice. *J. Antimicrob Chemother* (2003) 51:379-384.

<sup>15</sup> Bauer et al. An antimicrobial stewardship program's impact with rapid polymerase chain reaction methicillin-resistant *Staphylococcus aureus*/*S. aureus* blood culture test in patients with *S. aureus* bacteremia. *Clin Infect Dis* (2010) vol. 51 (9) pp. 1074-80

<sup>16</sup> Brown and Paladino. Impact of rapid methicillin-resistant *Staphylococcus aureus* polymerase chain reaction testing on mortality and cost effectiveness in hospitalized patients with bacteraemia: a decision model. *Pharmacoeconomics* (2010) vol. 28 (7) pp. 567-75

Today, there are no diagnostic tests that can provide antibiotic susceptibility testing (AST) results within hours of a positive blood culture and Gram stain. Currently available molecular and antibody tests detect resistance markers, but these markers are not reliable indicators of susceptibility. Recent data have also shown that the available PCR molecular tests are subject to significant false positive and false negative results (4.9-12.9%) which may limit their utility<sup>17, 18</sup>.

The MicroPhage MRSA/MSSA Blood Culture Test provides Staph aureus identification and phenotypic determination of methicillin resistance and susceptibility that conforms to the guidance issued by the Clinical and Laboratory Standards Institute (CLSI). MSSA, MRSA and 'not SA' results are delivered within 5.5 hours of positive blood culture and are accomplished with minimal hands-on time.



To perform the test, a sample of the positive blood culture is added to each of the two provided reaction tubes, each comprised of proprietary bacteriophage and reagents. One tube (Blue) performs *S. aureus* identification. The second tube (Red) performs susceptibility testing. Following incubation, a small amount of the sample from each tube is dropped onto the Detector in each appropriate well. Identification is determined by the development of a test line that contains anti-bacteriophage antibodies in the Blue ID Window. Susceptibility or resistance is read on the test line in the Red RS Window.

The MicroPhage MRSA/MSSA Blood Culture Test is also unique in that it requires no special instrumentation and is easy enough to be run by any trained individual on any work shift, making it available to all hospitals and feasible to run on a 24/7 basis.

### Economic & Mortality Analysis

Timely and appropriate use of antibiotics in bacteremia is associated with reduced mortality and decreased length of stay (LOS). Lodise et al found that delayed treatment by any antibiotic for Staph aureus BSI patients resulted in a 5.9 day increase in LOS (20.2 days vs. 14.3 days)<sup>19</sup>. Shime et al found that MRSA patients receiving appropriate therapy within 48 hours of blood draw had a mortality rate of 6%, compared to 50% mortality for those receiving appropriate treatment only after 48 hours<sup>20</sup>. Bauer

<sup>17</sup> Blanc et al. High Proportion of Wrongly Identified Methicillin-Resistant *Staphylococcus aureus* Carriers by Use of a Rapid Commercial PCR Assay Due to Presence of Staphylococcal Cassette Chromosome Element Lacking the *mecA* Gene. J. Clin Micro (2011) 722-724

<sup>18</sup> Stamper et al. Genotypic and Phenotypic Characterization of Methicillin-Susceptible *Staphylococcus aureus* Isolates Misidentified as Methicillin-Resistant *Staphylococcus aureus* by the BD GeneOhm™ MRSA Assay. J. Clin Micro (2011) online publication.

<sup>19</sup> Lodise et al. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. CID 2003 Jun 1;36 (11):1418-23. Epub 2003 May 20

<sup>20</sup> Shime et al. The importance of a judicious and early empiric choice of antimicrobial for methicillin-resistant *Staphylococcus aureus* bacteraemia. Eur J Clin Microbiol Infect Dis (2010) vol. 29 (12) pp. 1475-9

et al showed that reducing the time to optimal antibiotic therapy (switch from empiric vancomycin to cefazolin or nafcillin in patients with methicillin-susceptible *S. aureus* bacteremia) by an average of 1.7 days resulted in a 6.2 day reduction in LOS<sup>21</sup>.

*Assumptions:* Assume the average mid-size hospital produces 75 positive blood culture samples that are also Gram positive cocci in clusters. The average patient has 2.2 blood culture sets drawn so the 75 samples equates to 34 patients. In a normal European or U.S. population 30% or 10 of these patients would have infections caused by Staph aureus. At a common MRSA prevalence rate of 50%, 5 cases would be MSSA and 5 would be MRSA.

*Cost Savings:* Utilizing the 4:1 LOS savings ratio reported by Bauer above, if the 5 MSSA patients could be transitioned from vancomycin to nafcillin just 3 days earlier, 15 hospital days could be eliminated. Most of these patients are in the ICU and would be moved to lower cost beds to continue recovery. The cost savings would be calculated based on a weighted average of ICU and step-down unit costs per day. Conservatively assuming this cost is only \$1000/day, a savings of \$15,000 would be realized. Note that since ICU space is often fully occupied, there is great value in vacating those beds early to allow for additional patients.

MRSA patients will also benefit from earlier results. Many (50%) are not receiving appropriate antibiotic therapy at the time of a positive blood culture. The use of this test would ensure that patients receive the most appropriate MRSA therapy in a timely manner. Not only would more MRSA patients be put on an appropriate antibiotic, but patients on vancomycin could be switched to other drugs if desired. Daptomycin, for example, is better-tolerated than vancomycin, and does not require a central line or therapeutic monitoring.

*Mortality Reduction in MSSA and MRSA patients:* The mean mortality rate for *S. aureus* BSI's is approximately 35%<sup>22, 23</sup>. Although definitive prospective studies remain to be done, the retrospective studies cited above suggest that faster implementation of appropriate antibiotic therapy has the potential to reduce mortality by one-third to one-half of its current level. Faster antimicrobial susceptibility testing is only one part of the solution: after the test results are obtained, they must be communicated and implemented as soon as possible. Thus, coordination between lab directors, pharmacists and treating physicians is critical.

Accelerated susceptibility testing thus represents a new paradigm and a significant advance in treating bacterial infectious disease patients. Properly implemented, it has the potential to save thousands of lives and billions of dollars.

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<sup>21</sup> Bauer et al. An Antimicrobial Stewardship Program's Impact with Rapid Polymerase Chain Reaction Methicillin Resistant Staphylococcus aureus/*S. aureus* Blood Culture Test in Patients with *S. aureus* Bacteremia. CID 2010:51, Nov

<sup>22</sup> Harbarth et al. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 2003 Nov; 115 (7):529-35

<sup>23</sup> Ibrahim et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000 Jul;118 (1):146-55