tain financial limits will be required to ensure ongoing health care for all — is key to developing the consensus necessary for cost control. I have witnessed this effect firsthand in Massachusetts, where for years our advocacy community focused exclusively on expanding coverage for medical expenditures and therefore opposed most initiatives that might have put that goal at risk, even those that might have meant controlling costs. Since Massachusetts passed its universal-coverage plan, this powerful advocacy community has shifted its attention to controlling costs as a means of preserving the program's affordability to the state. The result was the passage last year of an opening salvo in the cost-control wars here in Massachusetts — Senate bill 2526, An Act to Promote Cost Containment, Transparency and Efficiency in the Delivery of Quality Health Care. Other countries, such as the Netherlands and Switzerland, have demonstrated that it is possible to have both universal coverage (even coverage provided through private insurance companies) and much lower health care spending.

Thus, the choice between fixing our health insurance system and fixing our economy is a false one. A smart health care reform bill, which has at its center universal health insurance coverage for our citizens, can improve both individual health and the economy's health, both today and in the long run.

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Antibiotic-Resistant Bugs in the 21st Century — A Clinical Super-Challenge

Cesar A. Arias, M.D., Ph.D., and Barbara E. Murray, M.D.

In March 1942, a 33-year-old woman lay dying of streptococcal sepsis in a New Haven, Connecticut, hospital, and despite the best efforts of contemporary medical science, her doctors could not eradicate her bloodstream infection. Then they managed to obtain a small amount of a newly discovered substance called penicillin, which they cautiously injected into her. After repeated doses, her bloodstream was cleared of streptococci, she made a full recovery, and she went on to live to the age of 90.[1] Sixty-six years after her startling recovery, a report[2] described a 70-year-old man in San Francisco with endocarditis caused by vancomycin-resistant *Enterococcus faecium* (VRE). Despite the administration, for many days, of the best antibiotics available for combating VRE, physicians were unable to sterilize the patient's blood, and he died still bacteremic. We have come almost full circle and arrived at a point as frightening as the preantibiotic era: for patients infected with multidrug-resistant bacteria, there is no magic bullet.

It is difficult to imagine undertaking today's surgical procedures, transplantations, cancer chemotherapy, or care of the critically ill or HIV-infected without effective antimicrobial agents. Bacteria are champions of evolution, and a few microbes have adapted to a point where they pose serious clinical challenges for humans. Among the gram-positive organisms, methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. faecium* represent the biggest therapeutic hurdles (see table). The evolution of MRSA exemplifies the genetic adaptation of an organism into a first-class multidrug-resistant pathogen. After the introduction of penicillin and, later, methicillin, *S. aureus* quickly developed resistance to these β-lactam compounds, and by 2003, more than 50% of *S. aureus* isolates recovered in U.S. hospitals were MRSA.

Then MRSA began developing resistance to glycopeptides, first evolving, through largely undefined mutations, low-level resistance to vancomycin, which was associated with a thickening of the pathogen's cell walls. Such isolates were designated VISA (or GISA), for vancomycin (or glycopeptide) intermediately resistant *S. aureus* (see diagram). VISA is difficult for clinical laboratories to detect, but its presence is associated with the therapeutic failure of glycopeptides. The breakpoints for susceptibility to vancomycin have therefore been changed, screening tests for VISA have been proposed, and much debate has ensued regarding the usefulness of vancomycin in the treatment of serious MRSA infections.

Next, strains of MRSA with true, high-level resistance to vancomycin (vancomycin-resistant *S. aureus*, or VRSA) emerged. Such resistance is due to the acquisition of the *vanA* gene cluster, originally described in enterococci. Fortunately, fewer than a dozen such isolates have been reported (mostly in Michigan), and their dissemination appears to be limited, at least for now. VRSA, like other strains of health care–associated MRSA, is often resistant to multiple drugs, including clindamycin, aminoglycosides, trimethoprim–sulfamethoxazole, rifampin, and fluoroquinolones.

MRSA has also recently emerged as an important cause of infections outside hospitals. Community-associated MRSA is now the leading cause of identifiable skin and soft-tissue infections seen in U.S. emergency rooms. Such MRSA frequently causes severe infections resembling spider bites, as well as severe necrotizing fasciitis and pneumonia, and it often produces toxins such as the Panton–Valentine leukocidin and cytolytic peptides. It has also acquired genes that may increase its ability to survive. A single clone, USA300, is responsible for most community-associated MRSA infections in the United States.[3] Although such MRSA is commonly susceptible to oral antibiotics such as clindamycin, fluoroquinolones, trimethoprim–sulfamethoxazole, tetracyclines, and rifampin, some multidrug-resistant strains are emerging.

Though less virulent than MRSA, enterococci have long represented therapeutic problems, initially because of their "tolerance" to penicillin and vancomycin (which inhibit but don't kill them). Enterococci are the third most common cause of infective endocarditis, and the effect of penicillin tolerance on therapeutic outcomes was apparent by the late 1940s, when it became routine to add an aminoglycoside to penicillin in treating this disease. High-level resistance to all aminoglycosides is increasing, however, so that the synergistic and bactericidal activity of the combination of a cell-wall agent and an aminoglycoside is no longer effective against some isolates of enterococci from endocarditis.

More worrisome is the increased occurrence of *E. faecium* infections, since the majority of *E. faecium* isolated in U.S. critical care units is now resistant to vancomycin (more than 90% of VRE isolates in the United States are *E. faecium*) and to ampicillin (almost 100% of isolates are resistant), with some strains having developed resistance to the newer antibiotics as well. No appropriate therapy for VRE endocarditis has been defined,[4] and no agent has been approved by the Food and Drug Administration for this indication. The emergence of multidrug-resistant *E. faecium* correlates with the predominance of a single genetic lineage worldwide; members of this lineage have acquired genetic determinants that appear to increase their success in the hospital environment, and some have developed resistance to practically all available antibiotics.

Despite the recent dramatic reduction in antibiotic research by pharmaceutical companies, several compounds have been developed or resurrected to treat gram-positive infections. However, the available agents have important limitations: none have been shown to work better than vancomycin against MRSA; quinupristin–dalfopristin and linezolid have important toxic effects, and resistance to each has been observed (including linezolid-resistant VRE in patients who have never received the drug); daptomycin has sometimes failed against MRSA and enterococci, and resistance to it has emerged; and there are few data regarding tigecycline for enterococcal infections, and its low blood levels raise concern about its use in bacteremia. Among the agents in late stages of clinical development, the new cephalosporins (ceftobiprole and ceftaroline) will not be clinically useful against ampicillin-resistant *E. faecium*; dalbavancin, telavancin, and oritavancin will have important limitations for the treatment of vancomycin-resistant organisms; and although iclaprim may have a role in MRSA infections, its clinical usefulness against enterococci has not been demonstrated.

The situation is even more dire when it comes to nosocomial gram-negative infections, since no new antibiotics against these multidrug-resistant organisms are in advanced stages of clinical de-

Multidrug-Resistant Bacterial Organisms Causing Major Clinical Problems.*

Organism and Antibiotic Resistance	Common Mechanism of Resistance	Recent, Resurrected, and Future Antimicrobial Agents with Potential Clinical Use
Hospital-associated MRSA†		
Vancomycin (both VISA and VRSA)	Thickening of cell wall (not fully elucidated); change in the last amino acid of peptidoglycan precursors	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Daptomycin	Associated with changes in cell wall and cell membrane (not fully elucidated)	Linezolid, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Linezolid	Mutations in the 23S ribosomal RNA genes; rarely, acquisition of a methyltransferase gene (*cfr*)	Daptomycin, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Vancomycin-resistant *Enterococcus faecium*‡		
Ampicillin (common)	Mutation and overexpression of *pbp5*	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline
High-level resistance to aminoglycosides	Acquisition of aminoglycoside-modifying enzymes; ribosomal mutations (streptomycin)	No alternative for a reliable bactericidal effect alone or in combination
Linezolid	Mutations in the 23S ribosomal RNA genes	Quinupristin–dalfopristin, daptomycin, tigecycline
Daptomycin	Unknown	Linezolid, quinupristin–dalfopristin, tigecycline
Quinupristin–dalfopristin	Enzymes that inactivate quinupristin–dalfopristin, target modification	Daptomycin, linezolid, tigecycline
Escherichia coli, klebsiella species, and enterobacter species§		
Oxyimino-cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and cefepime)	Extended-spectrum β-lactamases (includes hyperproduction of the AmpC enzymes by Enterobacteriaceae family)	Carbapenems, tigecycline
Carbapenems	Production of carbapenemases, decreased permeability	Polymyxins, tigecycline
Acinetobacter species¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins
Pseudomonas aeruginosa¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins

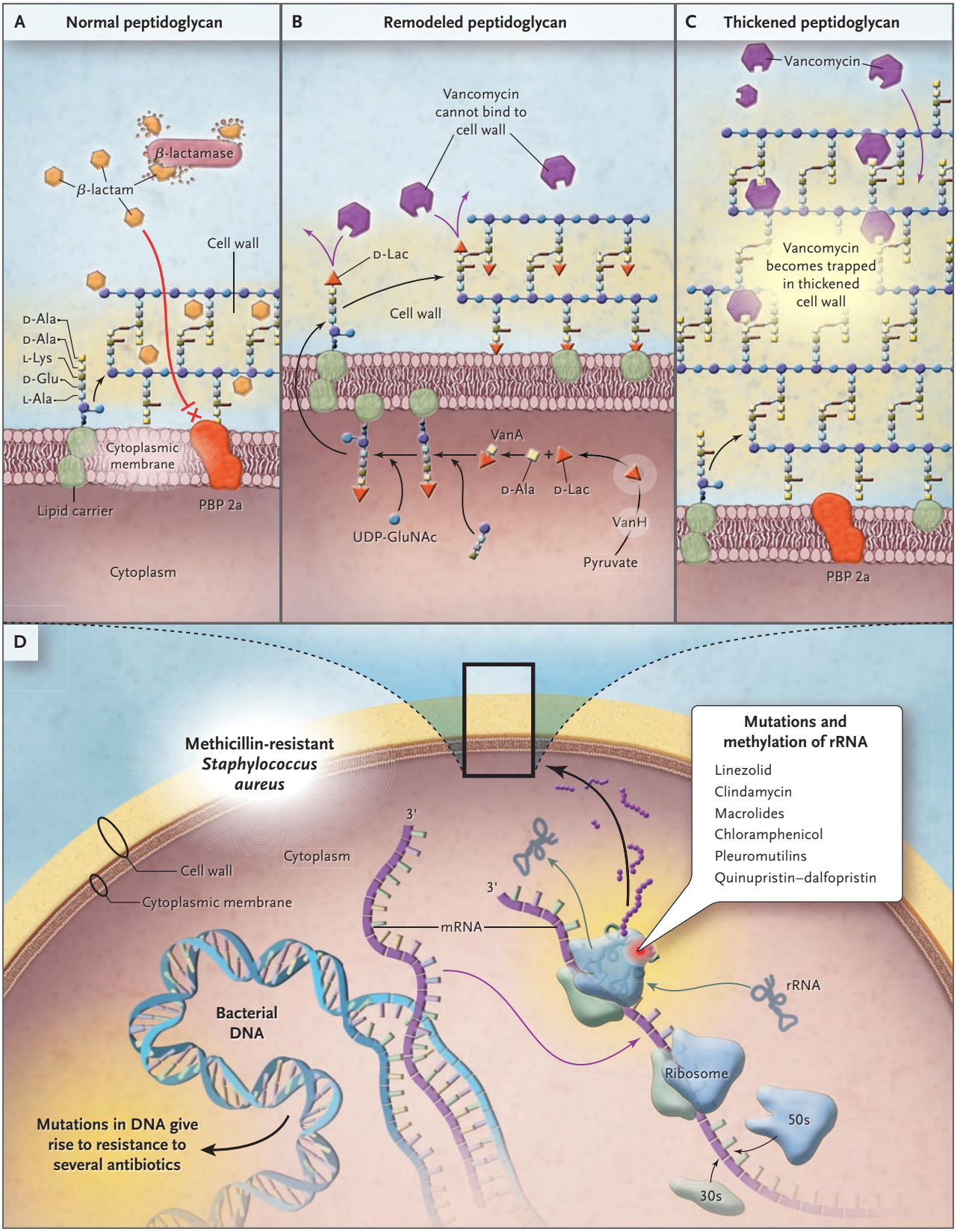
* The majority of listed antimicrobial agents have not been approved by the Food and Drug Administration (FDA) for the specified organisms, and clinical data on their efficacy are scarce. Ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, and iclaprim are not on the market yet. MRSA denotes methicillin-resistant *Staphylococcus aureus,* VISA *S. aureus* with intermediate susceptibility to vancomycin, and VRSA vancomycin-resistant *S. aureus*.

† Community-associated MRSA species are generally more susceptible than hospital-associated species to antibiotics, including trimethoprim–sulfamethoxazole, rifampin, quinolones, and clindamycin, though resistance to clindamycin may be selected during therapy if the organism carries an *erm* gene (encoding resistance to erythromycin); the laboratory should perform an antimicrobial-susceptibility disk test (i.e., a D-test) and inform the physician. Nonsusceptibility to daptomycin has been documented in some VISA strains.

‡ Linezolid and quinupristin–dalfopristin are FDA-approved for vancomycin-resistant *E. faecium* (VRE) infections. For VRE infections, aminoglycosides (gentamicin and streptomycin only) are used to obtain bactericidal synergistic activity when combined with β-lactams and glycopeptides; the synergistic effect is lost if the organism has a high level of resistance to aminoglycosides.

§ The use of tigecycline in gram-negative bacteremia has been questioned because of low serum levels and the emergence of resistance during therapy.

¶ The addition of rifampin to colistin has been shown to have some therapeutic benefit.



Common Mechanisms of Resistance in Methicillin-Resistant *Staphylococccus aureus*.

The top three panels depict a schematic magnification of the bacterial cell wall. In Panel A, resistance to β-lactam antibiotics in methicillin-resistant *Staphylococcus aureus* is caused by the production of a β-lactamase enzyme (penicillinase) and a low-affinity penicillin-binding protein (PBP) 2a. In Panel B, high-level resistance to glycopeptides is caused by the replacement of the last amino acid of peptidoglycan precursors (D-alanine [D-Ala] to D-lactate [D-Lac]). In Panel C, low-level resistance to glycopeptides is associated with increased synthesis of peptidoglycan, "trapping" the antibiotic in outer layers and preventing its interaction with precursors exiting the cytoplasm through the cell membrane. In Panel D, mechanisms of resistance involve mutations or modifications in either the DNA or ribosomal RNA (rRNA). D-Glu denotes D-glutamate, L-Lys L-lysine, and UDP-GluNAc uridine diphosphate *N*-acetylglucosamine.

velopment. Though multidrug-resistant *Pseudomonas aeruginosa* and acinetobacter are the best-known therapeutic challenges among the gram-negative bacteria (e.g., multidrug-resistant acinetobacter species are causing enormous challenges in soldiers returning from Iraq and Afghanistan), resistance to the most potent antibiotics has recently extended to members of the Enterobacteriaceae family, including hospital-associated strains of klebsiella, *Escherichia coli*, and enterobacter. Equally worrisome is the fact that multidrug-resistant gram-negative organisms have been found in otherwise healthy patients outside of hospitals — for instance, urinary tract infections caused by *E. coli* that is resistant to trimethoprim–sulfamethoxazole, fluoroquinolones, or both and that produce extended-spectrum β-lactamases (enzymes capable of destroying the most potent cephalosporins),[5] and recent major outbreaks of food poisoning caused by multidrug-resistant salmonella.

A slide show is available at NEJM.org

Until recently, carbapenems, such as imipenem, were almost uniformly active against resistant gram-negative organisms, but some strains have now developed very effective ways to deal with the carbapenems, including the production of β-lactamases (designated carbapenemases) that demolish the carbapenems; changes in outer-membrane porins that block the entry of these antibiotics; and active pumping of the antibiotic out of the cell using complex "efflux pumps." The situation is further complicated by the fact that the "permeability" barrier and efflux mechanisms also affect other classes of antibiotics (e.g., quinolones, aminoglycosides, and tigecycline). Moreover, the common presence of these β-lactamase genes of gram-negative bacteria in transferable mobile elements means that these genes could reach virtually any gram-negative bacterium and become a major threat in the future. Recognition of the presence of a carbapenemase in a gram-negative organism is of paramount importance, since strict infection-control measures are required to avert hospital epidemics and the dissemination of these genes to other gram-negative species.

Faced with this gloomy picture, 21st-century clinicians must turn to compounds developed decades ago and previously abandoned because of toxicity — or test everything they can think of and use whatever looks active. The resurrected polymixins (e.g., colistin with or without rifampin) are often the only available alternative for some pan-resistant gram-negatives, particularly acinetobacter, although toxicity (mainly renal) is still a problem, and reports of resistance are emerging.

It is more difficult than ever to eradicate infections caused by antibiotic-resistant "superbugs," and the problem is exacerbated by a dry pipeline for new antimicrobials with bactericidal activity against gram-negative bacteria and enterococci. A concerted effort on the part of academic researchers and their institutions, industry, and government is crucial if humans are to maintain the upper hand in this battle against bacteria — a fight with global consequences.

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