Title: Antibiotics and bacterial mechanisms of resistance

Authors:

Lucas T. Schulz, PharmD, BCPS AQ-ID
University of Wisconsin Health
Clinical Coordinator – Infectious Diseases
600 Highland Ave, MC 1530
Madison WI, 53792
Phone: 608-890-8617
Fax: 608-263-2494
Email: lschulz2@uwhealth.org

Ronald E. Kendall, PharmD, BCPS
Henry Ford Health System
Pharmacy Specialist – Infectious Diseases
2333 Biddle Avenue
Wyandotte, MI 48111
Phone: 734-246-9185
Fax: 734-246-6947

Corresponding author:
Lucas T Schulz, PharmD, BCPS AQ-ID
University of Wisconsin Health
Clinical Coordinator – Infectious Diseases
600 Highland Ave, MC 1530
Madison WI, 53792
Phone: 608-890-8617
Fax: 608-263-2494

Keywords/Index Terms: Antimicrobial resistance; beta-lactamases; vaborbactam; relebactam; omadacycline; eravacycline; plazomicin

Word Count: 2223

Abbreviations: AME - aminoglycoside-modifying enzymes, BL - β-lactam, BLI - β-lactamase inhibitors, CDC - Centers for Disease Control, CRE - carbapenem-resistant Enterobacteriaceae, ESBL - extended spectrum β-lactamase producing Enterobacteriaceae, FDA - Food and Drug Administration, MDR - Multidrug resistant, MIC - minimum inhibitory concentrations, MRSA - methicillin-resistant *Staphylococcus aureus,* VRE - vancomycin-resistant Enterococcus, XDR - extensively drug resistant, WHO - World Health Organization

Learning Objectives:

1) Recognize the global, national, and local impact of resistant bacteria.
2) Describe recent legislative changes to encourage new drug development.
3) Describe the most common mechanism of resistance, β-lactamase production.
4) Develop a treatment strategy for infections caused by extended-spectrum β-lactamase pathogens, multi-drug resistant *Pseudomonas aeruginosa*, and carbapenem-resistant Enterobacteriaceae.

This manuscript received no research support

LTS serves on an advisory board for The Medicines Company. REK has no financial COI to disclose.

Abstract/CE statement:

Infections resistant to many or all antimicrobials are occurring globally, nationally, and locally. Resistance is mediated through common, and often communicable, mechanisms and has eliminated many antibiotics from the treatment armamentarium. New antimicrobial agents have been developed to address new resistance mechanisms. Effectively combating antimicrobial resistance requires that we recognize its complex and extensive impact, encourage and legislate for new antimicrobial development, and establish treatment strategies for infections caused by antimicrobial resistant pathogens.

Antimicrobial resistance is a national and global problem that results in significant morbidity and mortality.[1] Resistant microbes include bacteria, viruses, parasites, and fungi and varies by geographic region. The World Health Organization (WHO) estimates that in 2016, almost a half million people developed multi-drug resistant tuberculosis globally with most new cases occurring in south Asia, including China and India.[2] A separate WHO report notes that resistance in *Plasmodium falciparum* to antimalarial medicines, including the new agent artemisinin, is increasing.[3] Malaria treatment failure rates are between 30% and 60% in the Western Pacific Region and threaten to negate the progress towards eradicating malaria world-wide.[3] Resistant pathogens, including drug resistant bacteria, are not limited by geographical or political boundaries, especially in the age of global travel.

The Centers for Disease Control (CDC) estimates that two million people in the United States are infected with drug resistant pathogens annually.[4] These pathogens result in the death of 23,000 patients each year. Contrary to the WHO report, drug-resistant malaria and drug-resistant HIV are excluded from this CDC report, likely due to low prevalence and ability of the US health system to absorb increased costs associated with alternative therapies. The cost of antibiotic resistance to the United States is estimated to exceed $20 billion dollars.[5]

Multidrug resistant (MDR) and extensively drug resistant (XDR) Gram-positive and Gram-negative bacteria account for 99.7% of the pathogens in the CDC report.[4] Pathogens with the highest concern for mortality include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus (VRE), pan-resistant *Streptococcus pneumoniae*, extended spectrum β-lactamase producing Enterobacteriaceae (ESBL), carbapenem-resistant Enterobacteriaceae (CRE), and multidrug resistant *Acinetobacter*. Mortality associated with highly drug resistant organisms is reported as high as 50% with transmission occurring rapidly.[6,7]

Recently, a London hospital experienced an outbreak of carbapenem-resistant *Klebsiella pneumoniae* that expressed colistin resistance and spread to forty patients in two hospitals over a 10 month period.[8] The outbreak was mitigated by rapid identification of the outbreak strain and good infection control practice response. Unfortunately, the spread of antibiotic resistance is difficult to control due to its multifaceted nature. Resistance is directly influenced by antibiotic use and misuse, human-to-human transmission, and transmission from the food chain to humans.[4]

Alexander Fleming, in his 1945 Nobel Laurate speech for the discovery of penicillin, warned of antimicrobial resistance;[9] however, until the late 20th century, new antibiotic discovery kept pace with resistance emergence. The Infectious Diseases Society of America (IDSA) forewarned of the impending resistance crisis in their 10 x '20 initiative.[10] In response to the diminishing antibiotic discovery pipeline, the IDSA called for ten new antibiotics by the year 2020. The initiative called for antibiotics directed at MRSA, VRE, ESBL, and CRE organisms which cause a disproportionate amount of hospital acquired infections.[11] In response to the national and global antimicrobial resistance epidemic, the Obama administration commissioned an antimicrobial resistance taskforce.[12] Taskforce recommendations were the basis for the national strategic plan to combat antimicrobial resistance.[13] The strategic plan addressed the antimicrobial resistance problem with a multipronged approach, including new drug development incentives and recommendations to implement antimicrobial stewardship programs in both the ambulatory and acute care medical practice settings. The CDC supplemented the call for increased role of antimicrobial stewardship programs when it outlined the seven core elements of inpatient antimicrobial stewardship and four core elements of ambulatory

stewardship.[14] These core elements now serve as the regulatory infrastructure for The Joint Commission accreditation and payment penalties for Medicare patient reimbursement.

Combating antimicrobial resistance requires a multifaceted approach, including clinicians, industry, agriculture, politicians, and patients. The remainder of this article will focus on two of these strategies: new drug development and repurposing available antibiotics. First, we will briefly describe common mechanisms of antibiotic resistance and, second, we will describe several new antibiotics and new treatment strategies to overcome the resistance mechanisms described.

Antimicrobial resistance mechanisms

Antimicrobial resistance occurs through at least one of eight separate mechanisms (Table 1).[15] For example, the composition of Gram-positive organisms' outer membrane eliminates some antibiotics ability to penetrate the cytoplasm, the site of antibacterial activity.[16] If an antimicrobial enters the cytoplasm or cell wall, local proteins may efflux[17] or degrade[18] it, rendering it ineffective against the organism. Alternatively, resistance may develop through alteration the antimicrobial target site (a process commonly seen in *Staphylococcus aureus* vancomycin resistance),[19] protection of the target site (a process common in *Neisseria spp.* tetracycline resistance),[20] or overproduction of the target site (a process common in trimethoprim-resistant bacteria).[21] Organisms possessing multiple mechanisms of resistance are known as multidrug-resistant organisms. If sufficient resistance mechanisms are acquired, the bacteria may become multidrug-resistant or even pan-resistant, where it lacks susceptibility to physiologically-safe antimicrobial therapy.

Bacteria adapt, share, and acquire various resistance mechanisms. The most common and concerning resistance mechanism is the production of β-lactamase enzymes. β-lactamase enzymes hydrolyze the β-lactam ring and eliminate the antibiotic site of action. β-lactamases are classified by two mechanisms: molecular structure or functional characteristics.[18,22,23] The Ambler classification system organizes β-lactamases by active site amino acid structure and metal ion associated with the hydrolysis activity.[22] Three Ambler classes, A, C, and D, use serine while Ambler Class B use a divalent zinc ion to hydrolyze and deactivate the β-lactam ring.[18] Representative enzyme examples important to Gram-negative resistance are in Table 2.

Unfortunately, the introduction of β-lactam antibiotics has resulted in the rapid emergence of resistance mechanisms.[4] Following the introduction of ceftriaxone into clinical practice, ESBL activity was identified as a direct result of TEM and SHV plasmid-mediated β-lactamase genes and intrinsic *ampC* gene activity in Enterobacteriaceae.[24] Additional ESBL enzymes, including CTX-M and ampC β-lactamase hyperproducers have since been discovered. Clinicians recognized the danger of this emerging resistance phenomenon and increased carbapenem utilization in response.[24-26] Carbapenems are stable to the hydrolysis of ESBL and ampC enzymes. However, increased use of carbapenems resulted in the emergence of carbapenemase enzymes, including KPC, IMP, NDM, and OXA.

New Antibiotic's Role in Treating Antibiotic Resistant Bacteria

New antibiotics in the drug development pipeline are critical for our ability to combat advanced mechanisms of antimicrobial resistance in Gram negative bacteria. As of December 2017, there were 48 new antibiotics in the pipeline, but historically only 20% of these will end up being approved by the US Food and Drug Administration (FDA) for patient use.[27]

New β-lactamase inhibitor antibiotics:

The use of β-lactam antibiotics was rapidly hindered by the development of β-lactamase enzymes which hydrolyze and deactivate the β-lactam ring. As a result, β-lactamase inhibitors (BLI) were developed and added to β-lactam (BL) antibiotics in a combination product (BL/BLI), such as ampicillin/sulbactam or piperacillin/tazobactam. Early BLIs were only effective against Ambler Class A, serine-based, β-lactamases. The companion β-lactam antibiotic is responsible for the antibacterial activity once the β-lactamase enzyme is inhibited.

Currently, 2100 different β-lactamases with various functional properties are identified and only five BLIs are approved for treatment in the United States: clavulanic acid, sulbactam, tazobactam, avibactam, and vaborbactam.[28] Clavulanic acid acts as a β-lactam-like compound and has the narrowest spectrum of inhibition. Sulbactam possesses a 6-desaminopenicillin sulfone and is slightly more broad than clavulanic acid, but less potent. Tazobactam is a penicillanic acid sulfone with similar spectrum of activity as sulbactam but higher potency. Avibactam is the first non-β-lactam-based BLI and significantly expands the inhibition spectrum to include some class C and D β-lactamases, in addition to class A.[29] Notably, between one and five avibactam molecules are required to inhibit a single β-lactamase molecule, whereas over 50 molecules of tazobactam or clavulanic acid are required for the same activity. The final BLI, vaborbactam, is also a non-β-lactam-based BLI that restores activity of its companion β-lactam (meropenem) against Enterobacteriaceae spp. that contain the KPC enzymes. In a novel mechanism, vaborbactam forms a reversible, covalent bond with the serine active site on the KPC enzyme.[30] The novel action of avibactam and vaborbactam are exploited when combined with ceftazidime and meropenem, respectively, and provide two treatment regimens for

extremely-drug-resistant, carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*.

Two additional BLIs are nearing the end of the antibiotic pipeline and expect FDA approval: relebactam and zidebactam. Relebactam is similar to avibactam, with activity against Ambler class A and C enzymes.[31] In phase II studies it has been combined with imipenem, leading to enhanced activity against imipenem-resistant strains of *Klebsiella pneumoniae* (producing ESBLs and/or KPCs) and *Pseudomonas aeruginosa* (overexpressing AmpC and/or lacking the OrpD porin).[32] Imipenem-relebactam recently underwent *in vitro* testing against a large collection of Gram-negative bacteria collected from across the United States in 2015 as part of the Study for Monitoring Antimicrobial Resistance Trends.[33] The addition of relebactam to imipenem increased the percentage susceptible from 70.3 to 94.2% for *P. aeruginosa*, from 96.1 to 99% for *K. pneumoniae*, from 98 to 100% for *Enterobacter* spp., and did not affect *A. baumannii* susceptibility, confirming its lack of activity against Ambler class D OXA-type enzymes. Zidebactam is a novel β-lactam enhancer designed specifically to augment penicillin-binding protein (PBP) 2 binding in *P. aeruginosa* and *A. baumannii*.[34] When combined with cefepime, which strongly inhibits PBP1 and PBP3, the improved bactericidal action seen is proposed to be due to the combined effect of saturated PBP1, PBP2, and PBP3. In vitro testing has demonstrated this potent combination is even capable of fully eradicating Ambler class B metallo-β-lactamase producing strains of *P. aeruginosa*.[35] High PBP2 binding affinity was also seen against *A. Baumannii*, and the combination of cefepime and zidebactam *in vitro* was able to completely eradicate *A. Baumannii* harboring an Ambler class D OXA-23 carbapenemase.[36]

New tetracycline-based antibiotics: Omadacycline and Eravacycline

Tetracyclines such as tetracycline, doxycycline, and minocycline have been in use for decades, leading to the emergence of tetracycline-resistant antibiotics.[17] Omadacycline contains a novel aminomethyl group attached to the traditional tetracycline structure, resulting in enhanced binding to the bacterial 30S ribosomal subunit and arresting bacterial protein synthesis.[37] Omadacycline remains active against bacterial strains expressing both ribosomal protection (target modification) and efflux resistance genes, thus providing activity against ESBL and carbapenemase-producing Enterobacteriaceae, *Acinetobacter* spp., and *Stenotrophomonas maltophilia.*[38] Omadacycline maintains activity in Gram-negative bacteria containing the efflux *tet*(B) gene and the target site modification *tet(O)* and *tet(M)* genes.[39] In a 2016 report from the SENTRY antimicrobial surveillance program, omadacycline showed in vitro activity against most Enterobacteriaceae isolates with 8% inhibition at ≤ 4 mg/L. *Proteus mirabilis,* indole-positive *Proteus* sp., and tigecycline-resistant *Klebsiella pneumoniae* were omadacycline-resistant.[38] Tetracycline-resistant Enterobacteriaceae generally displayed sensitive minimum inhibitory concentrations (MICs) to omadacycline, but with 2-4 fold higher MIC_{50} and MIC_{90} than tetracycline-susceptible isolates. *Pseudomonas aeruginosa* and *Providencia* spp. have high MICs to omadacycline (MIC >16 mg/L).

Eravacycline is a novel, fully synthetic tetracycline class antibiotics which adds a fluorine atom and a pyrrolidinoacetamido group to the traditional tetracycline structure.[40] These modifications result in activity against bacterial strains expressing both ribosomal protection and efflux resistance genes. Against 2213 Gram-negative bacterial pathogens in the 2014-2015 CANWARD surveillance study, eravacycline demonstrated activity against ESBL- and carbapenemase-producing *Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis,* and was generally twice as potent as tigecycline.[40] It should be noted that dosing leads to serum

concentrations of eravacycline that are approximately 300% higher than what current FDA-approved tigecycline dosing achieves. Eravacycline was also active against *Stenotrophomonas maltophilia and Acinetobacter* spp., including carbapenem-resistant *Acinetobacter baumannii,* which have acquired an OXA carbapenem-hydrolyzing class D β-lactamase, upregulated OXA-51, or an acquired metallo-β-lactamase. Eravacycline also lacks activity against *Pseudomonas aeruginosa.*

New Aminoglycoside Antibiotic: Plazomicin

The aminoglycoside class of antibiotics target the bacterial 30s ribosomal subunit and inhibit protein synthesis. Aminoglycoside resistance is attributed to a large and diverse class of proteins called aminoglycoside-modifying enzymes (AMEs) which inactivate the drug through acetylation, adenylylation, and phosphorylation.[41] In contrast to other aminoglycosides, plazomicin lacks important substituents that protect the molecule from many of the most common AMEs.[42] Plazomicin, however, may still be subject to resistance in *Pseudomonas aeruginosa* and *Acinetobacter* isolates that contain an upregulated amount of MexXY efflux pumps. Additionally, *Providencia stuartii* has a chromosomal AME and intrinsic outer membrane characteristics that provide resistance to all aminoglycosides. In an *in vitro* study of 110 CRE isolates of predominantly *Klebsiella pneumoniae* origin, plazomicin was potent against 100% of isolates with an MIC_{50} and MIC_{90} of 0.5 and 1 mg/L respectively, outperforming both gentamicin and aminoglycoside (81.8% and 23.6% susceptible, respectively).[43]

Summary

Antimicrobial resistance is increasing globally, nationally, and locally and is leading to significant associated morbidity and mortality. In response to a recent draught of novel antibiotics, the pharmaceutical industry has developed and the FDA approved several new

antibiotics. Unfortunately, the new antibiotics modify existing drugs and take advantage of known mechanisms of action. While their pharmacokinetics and pharmacodynamics are improved, lack of novel mechanisms of action inevitably will result in resistance. The clinician must use antibiotics wisely; this includes treating with appropriately broad empiric antibiotics, identifying a causative pathogen, and narrowing to targeted antibiotic therapy based on susceptibility testing and patient characteristics, such as allergies and organ function tests. New β-lactamase inhibitors, such as avibactam and vaborbactam, are currently available, while the new aminoglycoside plazomicin and new tetracycline-based therapies, omadacycline and eravacycline, expect FDA approval soon. The push and pull of antibiotic discovery and antibiotic resistance emergence will never cease; however, a multifaceted approach, including physicians, pharmacists, microbiologists, nurses, infection preventionists, and patients will be required to mitigate resistance emergence and maintain the efficacy of our current antimicrobial armamentarium.

References

1. World Health Organization [Internet]. Antimicrobial resistance: global report on surveillance 2014. c2014 [cited 2018 Feb 12]. Available from: http://wwwwhoint/drugresistance/documents/surveillancereport/en/.

2. World Health Organization [Internet]. Global Tuberculosis Report 2017. c2017 [cited 2018 Feb 12]. Available from: http://wwwwhoint/tb/publications/global_report/en/.

3. World Health Organization [Internet]. World Malaria Report 2017. c2017 [cited 2018 Feb 12]. Available from: http://wwwwhoint/malaria/publications/world-malaria-report-2017/en/.

4. Centers for Disease Control and Prevention [Internet]. Antibiotic Resistance Threats in the United States, 2013. c2013 [cited 2018 Feb 12]. Available from: https://www.cdc.gov/drugresistance/threat-report-2013/indexhtml.

5. Roberts RR, Hota B, Ahmad I, Scott RD, 2nd, Foster SD, Abbasi F, et al. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009 15;49(8):1175-84.

6. Centers for Disease C, Prevention. Vital signs: carbapenem-resistant Enterobacteriaceae. MMWR Morbidity and mortality weekly report. 2013 8;62(9):165-70.

7. Snitkin ES, Zelazny AM, Thomas PJ, Stock F, Group NCSP, Henderson DK, et al. Tracking a hospital outbreak of carbapenem-resistant Klebsiella pneumoniae with whole-genome sequencing. Science translational medicine. 2012 22;4(148):148ra16.

8. Otter JA, Doumith M, Davies F, Mookerjee S, Dyakova E, Gilchrist M, et al. Emergence and clonal spread of colistin resistance due to multiple mutational mechanisms in

carbapenemase-producing Klebsiella pneumoniae in London. Scientific reports. 2017 5;7(1):12711.

9. Fleming A. Penicillin: Nobel Laurate Lecture. December 11, 1945.

10. Infectious Diseases Society of A. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010 15;50(8):1081-3.

11. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009 1;48(1):1-12.

12. President's Council of Advisors on Science and Technology. Report to the President on Combating Antibiotic Resistance, September 2014. Available at obamawhitehouse.archives.gov.

13. National Action Plan for Combating Antibiotic-Resistant Bacteria. March 2015. Available at obamawhitehouse.archives.gov.

14. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014. Available at http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html.

15. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier; 2010.

16. Nikaido H, Vaara M. Molecular basis of bacterial outer membrane permeability. Microbiological reviews. 1985 49(1):1-32.

17. Srikumar R, Li XZ, Poole K. Inner membrane efflux components are responsible for beta-lactam specificity of multidrug efflux pumps in Pseudomonas aeruginosa. Journal of bacteriology. 1997 179(24):7875-81.

18. Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for beta-lactamases and its correlation with molecular structure. Antimicrobial agents and chemotherapy. 1995 39(6):1211-33.

19. Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in Staphylococcus aureus, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. Clinical microbiology reviews. 2010 23(1):99-139.

20. Morse SA, Johnson SR, Biddle JW, Roberts MC. High-level tetracycline resistance in Neisseria gonorrhoeae is result of acquisition of streptococcal tetM determinant. Antimicrobial agents and chemotherapy. 1986 30(5):664-70.

21. Huovinen P. Trimethoprim resistance. Antimicrobial agents and chemotherapy. 1987 31(10):1451-6.

22. Ambler RP. The structure of beta-lactamases. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 1980 16;289(1036):321-31.

23. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrobial agents and chemotherapy. 2010 54(3):969-76.

24. Pfeifer Y, Cullik A, Witte W. Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. International journal of medical microbiology : IJMM. 2010 300(6):371-9.

25. Bonnet R. Growing group of extended-spectrum beta-lactamases: the CTX-M enzymes. Antimicrobial agents and chemotherapy. 2004 48(1):1-14.

26. Caroff N, Espaze E, Gautreau D, Richet H, Reynaud A. Analysis of the effects of -42 and -32 ampC promoter mutations in clinical isolates of Escherichia coli hyperproducing ampC. The Journal of antimicrobial chemotherapy. 2000 45(6):783-8.

27. The Pew Charitable Trusts. Antibiotics currently in global clinical development. 2017. . Available at wwwpewtrustsorg/antibiotic-pipeline.

28. Bush K, Page MGP. What we may expect from novel antibacterial agents in the pipeline with respect to resistance and pharmacodynamic principles. Journal of pharmacokinetics and pharmacodynamics. 2017 44(2):113-32.

29. Bonnefoy A, Dupuis-Hamelin C, Steier V, Delachaume C, Seys C, Stachyra T, et al. In vitro activity of AVE1330A, an innovative broad-spectrum non-beta-lactam beta-lactamase inhibitor. The Journal of antimicrobial chemotherapy. 2004 54(2):410-7.

30. Hecker SJ, Reddy KR, Totrov M, Hirst GC, Lomovskaya O, Griffith DC, et al. Discovery of a Cyclic Boronic Acid beta-Lactamase Inhibitor (RPX7009) with Utility vs Class A Serine Carbapenemases. Journal of medicinal chemistry. 2015 14;58(9):3682-92.

31. Hirsch EB, Ledesma KR, Chang KT, Schwartz MS, Motyl MR, Tam VH. In vitro activity of MK-7655, a novel beta-lactamase inhibitor, in combination with imipenem against carbapenem-resistant Gram-negative bacteria. Antimicrobial agents and chemotherapy. 2012 56(7):3753-7.

32. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against Enterobacteriaceae and Pseudomonas aeruginosa. The Journal of antimicrobial chemotherapy. 2013 68(10):2286-90.

33. Lob SH, Hackel MA, Kazmierczak KM, Young K, Motyl MR, Karlowsky JA, et al. In Vitro Activity of Imipenem-Relebactam against Gram-Negative ESKAPE Pathogens Isolated by Clinical Laboratories in the United States in 2015 (Results from the SMART Global Surveillance Program). Antimicrobial agents and chemotherapy. 2017 61(6).

34. Livermore DM, Mushtaq S, Warner M, Vickers A, Woodford N. In vitro activity of cefepime/zidebactam (WCK 5222) against Gram-negative bacteria. The Journal of antimicrobial chemotherapy. 2017 72(5):1373-85.

35. Moya B, Barcelo IM, Bhagwat S, Patel M, Bou G, Papp-Wallace KM, et al. WCK 5107 (Zidebactam) and WCK 5153 Are Novel Inhibitors of PBP2 Showing Potent "beta-Lactam Enhancer" Activity against Pseudomonas aeruginosa, Including Multidrug-Resistant Metallo-beta-Lactamase-Producing High-Risk Clones. Antimicrobial agents and chemotherapy. 2017 61(6).

36. Moya B, Barcelo IM, Bhagwat S, Patel M, Bou G, Papp-Wallace KM, et al. Potent beta-Lactam Enhancer Activity of Zidebactam and WCK 5153 against Acinetobacter baumannii, Including Carbapenemase-Producing Clinical Isolates. Antimicrobial agents and chemotherapy. 2017 61(11).

37. Draper MP, Weir S, Macone A, Donatelli J, Trieber CA, Tanaka SK, et al. Mechanism of action of the novel aminomethylcycline antibiotic omadacycline. Antimicrobial agents and chemotherapy. 2014;58(3):1279-83.

38. Pfaller MA, Huband MD, Rhomberg PR, Flamm RK. Surveillance of Omadacycline Activity against Clinical Isolates from a Global Collection (North America, Europe, Latin America, Asia-Western Pacific), 2010-2011. Antimicrobial agents and chemotherapy. 2017 61(5).

39. Tanaka SK, Steenbergen J, Villano S. Discovery, pharmacology, and clinical profile of omadacycline, a novel aminomethylcycline antibiotic. Bioorganic & medicinal chemistry. 2016 24(24):6409-19.

40. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. International journal of antimicrobial agents. 2018 51(1):62-4.

41. Almaghrabi R, Clancy CJ, Doi Y, Hao B, Chen L, Shields RK, et al. Carbapenem-resistant Klebsiella pneumoniae strains exhibit diversity in aminoglycoside-modifying enzymes, which exert differing effects on plazomicin and other agents. Antimicrobial agents and chemotherapy. 2014 58(8):4443-51.

42. Aggen JB, Armstrong ES, Goldblum AA, Dozzo P, Linsell MS, Gliedt MJ, et al. Synthesis and spectrum of the neoglycoside ACHN-490. Antimicrobial agents and chemotherapy. 2010 54(11):4636-42.

43. Zhang Y, Kashikar A, Bush K. In vitro activity of plazomicin against beta-lactamase-producing carbapenem-resistant Enterobacteriaceae (CRE). The Journal of antimicrobial chemotherapy. 2017 72(10):2792-5.

Table 1: Mechanisms of antimicrobial resistance		
Target Site	**Movement Across Membrane**	**Other**
Target site alteration	Intracellular efflux	Metabolic process circumvention
Target site protection	Decreased permeability	Antimicrobial requisition
Target site overproduction		Enzymatic alteration

Table 2: Classification schemes of β-lactamase enzymes. Modified from Bush et al.(23)

Bolded enzymes in the Bush/Jacoby column are clinically important.

Ambler Classification	A	B	C	D
β-lactamase	Penicillinase	Metallo β-lactamase	Cephalosporinase	Oxacillinase
Bush/Jacoby classification	PC1, **TEM, SHV**, VEB, PER, PSE, CARB, RTG	**IMP, VIM, NDM,** IND, L1, CAU, GOB, FEZ	**AmpC**, ACT, CMY, FOX, MIR, CMY	**OXA**
Common phenotype	Extended spectrum β-lactamases	Carbapenemases	Extended spectrum β-lactamases	Carbapenemases