

ANTIMICROBIALS - I

NEWER ANTIBIOTICS

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Abstract: Antibiotics have revolutionised medical practice and their over zealous use has resulted in increased incidences of emerging resistant organisms. As newer molecules were identified especially for Gram negative organisms, many clinical trials were conducted. However, only few trials included children between 0 and 18 of age. Newer beta lactamase inhibitors were also recognized and they are first generation beta lactamase inhibitors with beta lactum rings, the second generation beta lactamase inhibitors with diaxabicyclooctane molecules and third generation beta lactamase are boronic acid compounds. Liberal and indiscriminate use of antibiotics have resulted in emergence of antibiotic resistance in the bacteriae with newer mechanisms, which in turn led on to higher medical costs and the increased mortality. Hence, there is a need for newer antibiotics and this article deals with antibiotics found in the last two decades and their uses.

Keywords: Antibiotics, Beta lactamase inhibitors, Synthetic aminoglycoside, Tetracyclines, Siderophore, Plazomycin, Ervacycline, Cefiderocol, Glycopeptides, Oxazolidinones.

Points to Remember

- Microbiological identification of infections should be the norm and newer drugs should not be used empirically.
- Excellent new drugs are available for ESBL producers.
- In India, carbapenamase producers are predominantly NDM and OXA-48 and to target this mechanism of resistance, more effective drugs are needed.
- Majority of the trials were conducted only in adults hence more data on the pharmacokinetics / pharmacodynamics of drugs are needed in children including newborns.
- Newer antibiotics should be reserved only for infections where there are limited therapeutic options.

References

1. Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, Anandan S, Ramasubramanian V, Swaminathan S, et al. Newer β -Lactam/ β -Lactamase inhibitor for multidrug-resistant gram-negative infections: Challenges, implications and surveillance strategy for India. Indian J Med Microbiol 2018; 36:334-343.
2. Tammaro PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America antimicrobial resistant treatment guidance: gram-negative bacterial infections. Clin Infect Dis 2020; 72(7):e169-e183.doi:10.1093/cid/ciaa1478.
3. Shirley M. Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative Bacterial Infections. Drugs 2018; 78:675-692.
4. Karaikos I, Galani I, Souli M, Giannarelli H. Novel β -lactam- β -lactamase inhibitor combinations: expectations for the treatment of carbapenem-resistant Gram-negative pathogens. Expert Opin Drug Metab Toxicol 2019; 15:133-149.
5. Kazmierczak KM, de Jonge BLM, Stone GG, Sahm DF. In vitro activity of ceftazidime/avibactam against isolates of Enterobacteriaceae collected in European countries: INFORM global surveillance 2012-15. J Antimicrob Chemother 2018; 73:2782-2788.

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6. Yasmin M, Fouts DE, Jacobs MR, Haydar H, Marshall SH, White R, et al. Monitoring Ceftazidime-Avibactam and Aztreonam Concentrations in the Treatment of a Bloodstream Infection Caused by a Multidrug-Resistant Enterobacter sp. Carrying Both Klebsiella pneumoniae Carbapenemase-4 and New Delhi Metallo-β-Lactamase-1. *Clin Infect Dis* 2020; 71:1095-1098.
7. Testa R, Cantón R, Giani T, Morosini M-I, Nichols WW, Seifert H, et al. In vitro activity of ceftazidime, ceftaroline and aztreonam alone and in combination with avibactam against European Gram-negative and Gram-positive clinical isolates. *Int J Antimicrob Agents* 2015; 45: 641-646.
8. Yahav D, Giske CG, Gråmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-Lactamase Inhibitor Combinations. *Clin Microbiol Rev* 2020; 34(1):e00115-20. <https://doi.org/10.1128/cmr.00115-20>
9. Horcajada JP, Montero M, Oliver A, Sorlí L, Luque S, Gómez-Zorrilla S, et al. Epidemiology and Treatment of Multidrug-Resistant and Extensively Drug-Resistant Pseudomonas aeruginosa Infections. *Clin Microbiol Rev* 2019;32(4):e00031-19.<https://doi.org/10.1128/CMR.00031-19>
10. Lizza BD, Betthauser KD, Ritchie DJ, Micek ST, Kollef MH. New Perspectives on Antimicrobial Agents: Ceftolozane-Tazobactam. *Antimicrob Agents Chemother* 2021;65:e0231820.
11. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI). *Clin Infect Dis* 2015; 60:1462-1471.
12. Novelli A, Del Giacomo P, Rossolini GM, Tumbarello M. Meropenem/vaborbactam: a next generation β-lactam β-lactamase inhibitor combination. *Expert Rev Anti-Infect Ther* 2020; 18:643-655.
13. Smith JR, Rybak JM, Claeys KC. Imipenem-Cilastatin-Relebactam: A Novel β-Lactam-β-Lactamase Inhibitor Combination for the Treatment of Multidrug-Resistant Gram-Negative Infections. *Pharmacotherapy* 2020; 40:343-356.
14. Mansour H, Ouweini AEL, Chahine EB, Karaoui LR. Imipenem/cilastatin/relebactam: A new carbapenem β-lactamase inhibitor combination. *Am J Health Syst Pharm* 2021; 78:674-683.
15. Heo YA. Imipenem/Cilastatin/Relebactam: A Review in Gram-Negative Bacterial Infections. *Drugs* 2021; 81:377-388.
16. Eljaaly K, Alharbi A, Alshehri S, Ortwine JK, Pogue JM. Plazomicin: A Novel Aminoglycoside for the Treatment of Resistant Gram-Negative Bacterial Infections. *Drugs* 2019; 79:243-269.
17. Livermore DM, Mushtaq S, Warner M, Zhang J-C, Maharjan S, Doumith M, et al. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant Enterobacteriaceae isolates. *J Antimicrob Chemother* 2011; 66:48-53.
18. Serio AW, Keepers T, Krause KM. Plazomicin is active against Metallo-β-Lactamase-Producing Enterobacteriaceae. *Open Forum Infect Dis* 2019, Volume 6, Issue 4, April 2019, ofz123, <https://doi.org/10.1093/ofid/ofz123>
19. Shaer KM, Zmarlicka MT, Chahine EB, Piccicacco N, Cho JC. Plazomicin: A Next-Generation Aminoglycoside. *Pharmacotherapy* 2019; 39:77-93.
20. Zhanel GG, Cheung D, Adam H, Zelenitsky S, Golden A, Schweizer F, et al. Review of Eravacycline, a Novel Fluorocycline Antibacterial Agent. *Drugs* 2016; 76:567-588.
21. Scott LJ. Eravacycline: A Review in Complicated Intra-Abdominal Infections. *Drugs* 2019; 79:315-324.
22. Zhao C, Wang X, Zhang Y, Wang R, Wang Q, Li H, et al. In vitro activities of Eravacycline against 336 isolates collected from 2012 to 2016 from 11 teaching hospitals in China. *BMC Infect Dis* 2019 Jun 10; 19(1):508. doi: 10.1186/s12879-019-4093-1.
23. Jacobs MR, Abdelhamed AM, Good CE, Rhoads DD, Hujer KM, Hujer AM, et al. ARGONAUT-I: Activity of Cefiderocol (S-649266), a Siderophore Cephalosporin, against Gram-Negative Bacteria, Including Carbapenem-Resistant Nonfermenters and Enterobacteriaceae with Defined Extended-Spectrum β-Lactamases and Carbapenemases. *Antimicrob Agents Chemother* 2019. <https://doi.org/10.1128/AAC.01801-18>.
24. Kresken M, Korte-Berwanger M, Gatermann SG, Pfeifer Y, Pfennigwerth N, Seifert H, et al. In vitro activity of cefiderocol against aerobic Gram-negative bacterial pathogens from Germany. *Int J Antimicrob Agents* 2020; 56:106128.
25. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* 2021; 21:226-240.
26. Trecarichi EM, Quirino A, Scaglione V, Longhini F, Garofalo E, Bruni A, et al. Successful treatment with cefiderocol for compassionate use in a critically ill patient with XDR *Acinetobacter baumannii* and KPC-producing *Klebsiella pneumoniae*: a case report. *J Antimicrob Chemother* 2019; 74:3399-3401.
27. Karaiskos I, Souli M, Galani I, Giannarellou H. Colistin: still a lifesaver for the 21st century? *Expert Opin Drug Metab Toxicol* 2017; 13:59-71.
28. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International consensus guidelines for the

- optimal use of the polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM) and Society of Infectious Diseases Pharmacists (SIDP). *Pharmacotherapy* 2019; 39:10-39.
29. Pontikis K, Karauskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. *Int J Antimicrob Agents* 2014; 43:52-59.
 30. Albur MS, Noel A, Bowker K, MacGowan A. The combination of colistin and fosfomycin is synergistic against NDM-1-producing Enterobacteriaceae in in vitro pharmacokinetic/pharmacodynamic model experiments. *Int J Antimicrob Agents* 2015; 46:560-567.
 31. Matzi V, Lindenmann J, Porubsky C, Kugler SA, Maier A, Dittrich P, et al. Extracellular concentrations of fosfomycin in lung tissue of septic patients. *J Antimicrob Chemother* 2010; 65:995-998.
 32. Pfausler B, Spiss H, Dittrich P, Zeitlinger M, Schmutzhard E, Joukhadar C. Concentrations of fosfomycin in the cerebrospinal fluid of neurointensive care patients with ventriculostomy-associated ventriculitis. *J Antimicrob Chemother* 2004; 53:848-852.
 33. Vardakas KZ, Legakis NJ, Triarides N, Falagas ME. Susceptibility of contemporary isolates to fosfomycin: a systematic review of the literature. *Int J Antimicrob Agents* 2016; 47:269-285.
 34. Dinh A, Salomon J, Bru JP, Bernard L. Fosfomycin: efficacy against infections caused by multidrug-resistant bacteria. *Scand J Infect Dis* 2012; 44:182-189.
 35. Garnacho-Montero J, Dimopoulos G, Poulakou G, Akova M, Cisneros JM, De Waele J, et al. Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU. *Intensive Care Med* 2015; 41:2057-2075.
 36. Giamarellou H, Poulakou G. Pharmacokinetic and pharmacodynamic evaluation of tigecycline. *Expert Opin Drug Metab Toxicol* 2011; 7:1459-1470.
 37. Burkhardt O, Rauch K, Kaever V, Hadem J, Kielstein JT, Welte T. Tigecycline possibly underdosed for the treatment of pneumonia: a pharmacokinetic viewpoint. *Int J Antimicrob Agents* 2009; 34:101-102.
 38. Bassetti M, Poulakou G, Giamarellou H. Is there a future for tigecycline? *Intensive Care Medicine* 2014; 40:1039-1045.
 39. White BP, Barber KE, Stover KR. Ceftaroline for the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Am J Health Syst Pharm* 2017; 74:201-208.
 40. Kosowska-Shick K, McGhee PL, Appelbaum PC. Affinity of ceftaroline and other beta-lactams for penicillin-binding proteins from *Staphylococcus aureus* and *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2010; 54:1670-1677.
 41. Scheeren TWL. Ceftobiprole medocaril in the treatment of hospital-acquired pneumonia. *Future Microbiol* 2015; 10:1913-1928.
 42. Gales AC, Sader HS, Jones RN. Antimicrobial activity of dalbavancin tested against Gram-positive clinical isolates from Latin American medical centres. *Clin Microbiol Infect* 2005; 11:95-100.
 43. Klinker KP, Borgert SJ. Beyond Vancomycin: The Tail of the Lipoglycopeptides. *Clin Ther* 2015; 37:2619-2636.
 44. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. *N Engl J Med* 2014; 370:2169-2179.
 45. Burdette SD, Trotman RX. Tedizolid: The First Once-Daily Oxazolidinone Class Antibiotic. *Clin Infect Dis* 2014; 61:1315-1321.
 46. Ferrández O, Urbina O, Grau S. Critical role of tedizolid in the treatment of acute bacterial skin and skin structure infections. *Drug Des Devel Ther* 2017; 11:65-82.
 47. Jorgensen SCJ, Mercuro NJ, Davis SL, Rybak MJ. Delafloxacin: Place in Therapy and Review of Microbiologic, Clinical and Pharmacologic Properties. *Infect Dis Ther* 2018; 7:197-217.
 48. Draper MP, Weir S, Macone A, Donatelli J, Trieber CA, Tanaka SK, et al. Mechanism of action of the novel aminomethylcycline antibiotic omadacycline. *Antimicrob Agents Chemother* 2014; 58:1279-1283.
 49. Villano S, Steenbergen J, Loh E. Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections. *Future Microbiol* 2016; 11:1421-1434.