Safety in pregnancy[498] has not been established for any of the quinolones, but studies of babies born to women exposed to norfloxacin or ciprofloxacin during the first trimester identified no increase in major malformations, stillbirths, or premature births.[543–545] In one prospective case-control study comparing 200 women exposed to fluoroquinolones and 200 women exposed to known nonembryotoxic antibiotics, there were no differences in birth defects, spontaneous abortions, prematurity, or fetal distress, but there was a higher rate of therapeutic abortions, suggesting that concerns about teratogenic risks may exceed the actual risks.[544] Because quinolones can be excreted in breast milk, they should be avoided for nursing mothers.

Key References

The complete reference list is available online at Expert Consult.

30. Hooper DC, Jacoby GA. Topoisomerase inhibitors: fluoroquinolone mechanisms of action and resistance. *Cold Spring Harb Perspect Med*. 2016.
55. Piddock LJV. Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. *Clin Microbiol Rev*. 2006;19:382–402.
95. Dudley MN. Pharmacokinetics of fluoroquinolones. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:115–132.
130. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious diseases society of America and the European society for microbiology and infectious diseases. *Clin Infect Dis*. 2011;52:e103–e120.
143. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *N Engl J Med*. 1991;324:384–394.
145. Schaeffer AJ, Nicolle LE. Clinical practice. Urinary tract infections in older men. *N Engl J Med*. 2016;374:562–571.
192. Bennish ML. Treatment and prophylaxis of gastroenteritis. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:193–216.
253. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guideline by the surgical infection society and the infectious diseases society of America. *Clin Infect Dis*. 2010;50:133–164.
329. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. *Clin Infect Dis*. 2016;63:e61–e111.
376. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371:1577–1587.
377. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med*. 2014;371:1588–1598.
378. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
400. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. *Clin Infect Dis*. 2011;52:e56–e93.
441. Knoll GA, Humar A, Fergusson D, et al. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. *JAMA*. 2014;312:2106–2114.
447. Low DE. Quinolone resistance and its clinical relevance. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:355–386.
479. Lautenbach E, Metlay JP, Bilker WB, et al. Association between fluoroquinolone resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections: the role of inadequate empirical antimicrobial therapy. *Clin Infect Dis*. 2005;41:923–929.
499. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Saf*. 2009;32:359–378.
530. Chou H-W, Wang J-L, Chang C-H, et al. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and β-lactam/β-lactamase inhibitors: a taiwanese nationwide study. *Clin Infect Dis*. 2015;60:566–577.

References

1. Domagala JM. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *J Antimicrob Chemother*. 1994;33:685–706.
2. Rolston KVI, Frisbee-Hume S, LeBlanc BM, et al. Antimicrobial activity of a novel des-fluoro (6) quinolone, garenoxacin (BMS-284756), compared to other quinolones, against clinical isolates from cancer patients. *Diagn Microbiol Infect Dis*. 2002;44:187–194.
3. Kappel EM, Shakibaei M, Bello A, et al. Effects of the des-f(6)-quinolone garenoxacin (BMS-284756), in comparison to those of ciprofloxacin and ofloxacin, on joint cartilage in immature rats. *Antimicrob Agents Chemother*. 2002;46:3320–3322.
4. Domagala JM, Hagen SE. Structure-activity relationships of the quinolone antibacterials in the new millennium: some things change and some do not. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:3–18.
5. Drlica K, Hooper DC. Mechanisms of quinolone action. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:19–40.
6. Wang JC. DNA topoisomerases. *Annu Rev Biochem*. 1996;65:635–692.
7. Drlica K, Zhao XL. DNA gyrase, topoisomerase IV, and the 4-quinolones. *Microbiol Rev*. 1997;61:377–392.
8. Kato J, Nishimura Y, Imamura R, et al. New topoisomerase essential for chromosome segregation in *E. coli*. *Cell*. 1990;63:393–404.
9. Ullsperger C, Cozzarelli NR. Contrasting enzymatic activities of topoisomerase IV and DNA gyrase from *Escherichia coli*. *J Biol Chem*. 1996;271: 31549–31555.
10. Aubry A, Fisher LM, Jarlier V, et al. First functional characterization of a singly expressed bacterial type II topoisomerase: the enzyme from *Mycobacterium tuberculosis*. *Biochem Biophys Res Commun*. 2006;348:158–165.
11. Wentzell LM, Maxwell A. The complex of DNA gyrase and quinolone drugs on DNA forms a barrier to the T7 DNA polymerase replication complex. *J Mol Biol*. 2000;304:779–791.
12. Willmott CJ, Critchlow SE, Eperon IC, et al. The complex of DNA gyrase and quinolone drugs with DNA forms a barrier to transcription by RNA polymerase. *J Mol Biol*. 1994;242:351–363.
13. Drlica K, Malik M, Kerns RJ, et al. Quinolone-mediated bacterial death. *Antimicrob Agents Chemother*. 2008;52:385–392.
14. Kreuzer KN, Cozzarelli NR. *Escherichia coli* mutants thermosensitive for deoxyribonucleic acid gyrase subunit a: effects on deoxyribonucleic acid replication, transcription, and bacteriophage growth. *J Bacteriol*. 1979;140:424–435.
15. Shen LL, Kohlbrenner WE, Weigl D, et al. Mechanism of quinolone inhibition of DNA gyrase. Appearance of unique norfloxacin binding sites in enzyme-DNA complexes. *J Biol Chem*. 1989;264:2973–2978.
16. Willmott CJ, Maxwell A. A single point mutation in the DNA gyrase a protein greatly reduces binding of fluoroquinolones to the gyrase-DNA complex. *Antimicrob Agents Chemother*. 1993;37:126–127.
17. Ng EY, Trucksis M, Hooper DC. Quinolone resistance mutations in topoisomerase IV: relationship of the flqa locus and genetic evidence that topoisomerase IV is the primary target and DNA gyrase the secondary target of fluoroquinolones in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 1996;40:1881–1888.
18. Pan XS, Fisher LM. Targeting of DNA gyrase in *Streptococcus pneumoniae* by sparfloxacin: selective targeting of gyrase or topoisomerase IV by quinolones. *Antimicrob Agents Chemother*. 1997;41:471–474.
19. Houssaye S, Gutmann L, Varon E. Topoisomerase mutations associated with in vitro selection of resistance to moxifloxacin in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2002;46:2712–2715.
20. Blanche F, Cameron B, Bernard FX, et al. Differential behaviors of *Staphylococcus aureus* and *Escherichia coli* type II DNA topoisomerases. *Antimicrob Agents Chemother*. 1996;40:2714–2720.
21. Pan XS, Fisher LM. DNA gyrase and topoisomerase IV are dual targets of clinafloxacin action in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 1998;42:2810–2816.
22. Ince D, Zhang X, Silver LC, et al. Dual targeting of DNA gyrase and topoisomerase IV: target interactions of garenoxacin (BMS-284756, t3811ME), a new desfluoroquinolone. *Antimicrob Agents Chemother*. 2002;46:3370–3380.
23. Drlica K, Malik M, Kerns RJ, et al. Quinolone-mediated bacterial death. *Antimicrob Agents Chemother*. 2008;52:385–392.
24. Dietz WH, Cook TM, Goss WA. Mechanism of action of nalidixic acid on *Escherichia coli*. III. Conditions required for lethality. *J Bacteriol*. 1966;91:768–773.
25. Kohanski MA, Dwyer DJ, Hayete B, et al. A common mechanism of cellular death induced by bactericidal antibiotics. *Cell*. 2007;130:797–810.
26. Lynn R, Giaever G, Swanberg SL, et al. Tandem regions of yeast DNA topoisomerase II share homology with different subunits of bacterial gyrase. *Science*. 1986;233:647–649.
27. Gootz TD, Osheroff N. Quinolones and eukaryotic topoisomerases. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:69–89.
28. Dong KC, Berger JM. Structural basis for gate-DNA recognition and bending by type IIA topoisomerases. *Nature*. 2007;450:1201–1205.
29. Hussy P, Maass G, Tummler B, et al. Effect of 4-quinolones and novobiocin on calf thymus DNA polymerase alpha primase complex, topoisomerases I and II, and growth of mammalian lymphoblasts. *Antimicrob Agents Chemother*. 1986;29:1073–1078.
30. Hooper DC, Jacoby GA. Topoisomerase inhibitors: fluoroquinolone mechanisms of action and resistance. *Cold Spring Harb Perspect Med*. 2016.
31. Hooper DC. Mechanisms of quinolone resistance. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:41–67.
32. Jacoby GA. Mechanisms of resistance to quinolones. *Clin Infect Dis*. 2005;41:S120–S126.
33. Tran JH, Jacoby GA. Mechanism of plasmid-mediated quinolone resistance. *Proc Natl Acad Sci USA*. 2002;99:5638–5642.
34. Wang M, Tran JH, Jacoby GA, et al. Plasmid-mediated quinolone resistance in clinical isolates of *Escherichia coli* from shanghai, China. *Antimicrob Agents Chemother*. 2003;47:2242–2248.
35. Robicsek A, Strahilevitz J, Jacoby GA, et al. Fluoroquinolone modifying enzyme: a novel adaptation of a common aminoglycoside acetyltransferase. *Nat Med*. 2006;12:83–88.
36. Périchon B, Courvalin P, Galimand M. Transferable resistance to aminoglycosides by methylation of G1405 in 16s rRNA and to hydrophilic fluoroquinolones by QepA-mediated efflux in *Escherichia coli*. *Antimicrob Agents Chemother*. 2007;51:2464–2469.
37. Yamane K, Wachino JI, Suzuki S, et al. New plasmid-mediated fluoroquinolone efflux pump, QepA, found in an *Escherichia coli* clinical isolate. *Antimicrob Agents Chemother*. 2007;51:3354–3360.
38. Hansen LH, Johannesen E, Burmolle M, et al. Plasmid-encoded multidrug efflux pump conferring resistance to olaquindox in *Escherichia coli*. *Antimicrob Agents Chemother*. 2004;48:3332–3337.
39. Ince D, Zhang X, Silver LC, et al. Topoisomerase targeting with and resistance to gemifloxacin in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2003;47:274–282.
40. Strahilevitz J, Hooper DC. Dual targeting of topoisomerase IV and gyrase to reduce mutant selection: direct testing of the paradigm by using WCK-1734, a new fluoroquinolone, and ciprofloxacin. *Antimicrob Agents Chemother*. 2005;49:1949–1956.
41. Hooper DC, Wolfson JS, Souza KS, et al. Genetic and biochemical characterization of norfloxacin resistance in *Escherichia coli*. *Antimicrob Agents Chemother*. 1986;29:639–644.
42. Yoshida H, Bogaki M, Nakamura M, et al. Quinolone resistance-determining region in the DNA gyrase *gyrB* gene of *Escherichia coli*. *Antimicrob Agents Chemother*. 1991;35:1647–1650.
43. Pan XS, Ambler J, Mehtar S, et al. Involvement of topoisomerase IV and DNA gyrase as ciprofloxacin targets in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 1996;40:2321–2326.
44. Poole K. Efflux-mediated resistance to fluoroquinolones in gram-negative bacteria. *Antimicrob Agents Chemother*. 2000;44:2233–2241.
45. Poole K. Efflux-mediated resistance to fluoroquinolones in gram-positive bacteria and the mycobacteria. *Antimicrob Agents Chemother*. 2000;44:2595–2599.
46. Okusu H, Ma D, Nikaido H. AcrAB efflux pump plays a major role in the antibiotic resistance phenotype of *Escherichia coli* multiple-antibiotic-resistance (Mar) mutants. *J Bacteriol*. 1996;178:306–308.
47. Murakami S, Nakashima R, Yamashita E, et al. Crystal structure of bacterial multidrug efflux transporter AcrB. *Nature*. 2002;419:587–593.
48. Wang H, Dzink-Fox JL, Chen MJ, et al. Genetic characterization of highly fluoroquinolone-resistant clinical *Escherichia coli* strains from China: role of *acrR* mutations. *Antimicrob Agents Chemother*. 2001;45:1515–1521.
49. Poole K, Tetro K, Zhao QX, et al. Expression of the multidrug resistance operon *mexA-mexB-oprM* in *Pseudomonas aeruginosa*: *mexR* encodes a regulator of operon expression. *Antimicrob Agents Chemother*. 1996;40:2021–2028.
50. Jalal S, Wretlind B. Mechanisms of quinolone resistance in clinical strains of *Pseudomonas aeruginosa*. *Microb Drug Resist*. 1998;4:257–261.
51. Masuda N, Sakagawa E, Ohya S, et al. Substrate specificities of MexAB-OprM, MexCD-OprJ, and MexXY-OprM efflux pumps in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2000;44:3322–3327.
52. Baucheron S, Imberechts H, Chaslus-Dancla E, et al. The AcrB multidrug transporter plays a major role in high-level fluoroquinolone resistance in *Salmonella enterica* serovar typhimurium phage type DT204. *Microb Drug Resist*. 2002;8:281–289.
53. Pradel E, Pagès JM. The AcrAB-TolC efflux pump contributes to multidrug resistance in the nosocomial pathogen *Enterobacter aerogenes*. *Antimicrob Agents Chemother*. 2002;46:2640–2643.
54. Kim HB, Wang M, Park CH, et al. *oqxAB* encoding a multidrug efflux pump in human clinical isolates of *Enterobacteriaceae*. *Antimicrob Agents Chemother*. 2009;53:3582–3584.
55. Piddock LJV. Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. *Clin Microbiol Rev*. 2006;19:382–402.
56. Yoshida H, Bogaki M, Nakamura S, et al. Nucleotide sequence and characterization of the *Staphylococcus aureus norA* gene, which confers resistance to quinolones. *J Bacteriol*. 1990;172:6942–6949.
57. Ng EY, Trucksis M, Hooper DC. Quinolone resistance mediated by *norA*: physiologic characterization and relationship to *flqB,* a quinolone resistance locus on the *Staphylococcus aureus* chromosome. *Antimicrob Agents Chemother*. 1994;38:1345–1355.
58. Truong-Bolduc QC, Strahilevitz J, Hooper DC. NorC, a new efflux pump regulated by MgrA of *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2006;50:1104–1107.
59. Truong-Bolduc QC, Dunman PM, Strahilevitz J, et al. MgrA is a multiple regulator of two new efflux pumps in *Staphylococcus aureus*. *J Bacteriol*. 2005;187:2395–2405.
60. Gill MJ, Brenwald NP, Wise R. Identification of an efflux pump gene, *pmrA,* associated with fluoroquinolone resistance in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 1999;43:187–189.
61. Brenwald NP, Gill MJ, Wise R. The effect of reserpine, an inhibitor of multidrug efflux pumps, on the in-vitro susceptibilities of fluoroquinolone-resistant strains of *Streptococcus pneumoniae* to norfloxacin. *J Antimicrob Chemother*. 1997;40:458–460.
62. Huang J, O'Toole PW, Shen W, et al. Novel chromosomally encoded multidrug efflux transporter MdeA in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2004;48:909–917.
63. Yamada Y, Hideka K, Shiota S, et al. Gene cloning and characterization of SdrM, a chromosomally-encoded multidrug efflux pump, from *Staphylococcus aureus*. *Biol Pharm Bull*. 2006;29:554–556.
64. Nakaminami H, Noguchi N, Sasatsu M. Fluoroquinolone efflux by the plasmid-mediated multidrug efflux pump QacB variant QacBIII in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2010;54:4107–4111.
65. Floyd JL, Smith KP, Kumar SH, et al. LmrS is a multidrug efflux pump of the major facilitator superfamily from *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2010;54:5406–5412.
66. Godreuil S, Galimand M, Gerbaud G, et al. Efflux pump lde is associated with fluoroquinolone resistance in *Listeria monocytogenes*. *Antimicrob Agents Chemother*. 2003;47:704–708.
67. Kaatz GW, DeMarco CE, Seo SM. MepR, a repressor of the *Staphylococcus aureus* MATE family multidrug efflux pump MepA, is a substrate-responsive regulatory protein. *Antimicrob Agents Chemother*. 2006;50:1276–1281.
68. Boncoeur E, Durmort C, Bernay B, et al. PatA and PatB form a functional heterodimeric ABC multidrug efflux transporter responsible for the resistance of *Streptococcus pneumoniae* to fluoroquinolones. *Biochemistry*. 2012;51:7755–7765.
69. Escudero JA, San MA, Gutierrez B, et al. Fluoroquinolone efflux in *Streptococcus suis* is mediated by SatAB and not by SmrA. *Antimicrob Agents Chemother*. 2011;55:5850–5860.
70. Martínez-Martínez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. *Lancet*. 1998;351:797–799.

71. Strahilevitz J, Jacoby G, Hooper DC, et al. Plasmid-mediated quinolone resistance: a multifaceted threat. *Clin Microbiol Rev*. 2009;22:664–689.
72. Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect Dis*. 2006;6:629–640.
73. Kim HB, Park CH, Kim CJ, et al. Prevalence of plasmid-mediated quinolone resistance determinants over a nine-year period. *Antimicrob Agents Chemother*. 2009;53:639–645.
74. Chávez-Jacobo VM, Hernández-Ramírez KC, Romo-Rodríguez P, et al. CrpP is a novel ciprofloxacin-modifying enzyme encoded by the *Pseudomonas aeruginosa* pUM505 plasmid. *Antimicrob Agents Chemother*. 2018;62:e02629–17.
75. Hansen LH, Jensen LB, Sørensen HI, et al. Substrate specificity of the OqxAB multidrug resistance pump in *Escherichia coli* and selected enteric bacteria. *J Antimicrob Chemother*. 2007;60:145–147.
76. Yamane K, Wachino J, Suzuki S, et al. New plasmid-mediated fluoroquinolone efflux pump, QepA, found in an *Escherichia coli* clinical isolate. *Antimicrob Agents Chemother*. 2007;51:3354–3360.
77. Eliopoulos CT, Eliopoulos GM. Activity in vitro of the quinolones. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:91–111.
78. Eliopoulos GM, Eliopoulos CT. Activity in vitro of the quinolones. In: Hooper DC, Wolfson JS, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology; 1993:161–193.
79. Wolfson JS, Hooper DC. Fluoroquinolone antimicrobial agents. *Clin Microbiol Rev*. 1989;2:378–424.
80. Jones RN, Fritsche TR, Sader HS. Antimicrobial activity of DC-159a, a new fluoroquinolone, against 1,149 recently collected clinical isolates. *Antimicrob Agents Chemother*. 2008;52:3763–3775.
81. Stern EJ, Uhde KB, Shadomy SV, et al. Conference report on public health and clinical guidelines for anthrax. *Emerg Infect Dis*. 2008;14:e1.
82. Aldred KJ, McPherson SA, Wang P, et al. Drug interactions with *Bacillus anthracis* topoisomerase IV: biochemical basis for quinolone action and resistance. *Biochemistry*. 2012;51:370–381.
83. Jacobs MR. Activity of quinolones against mycobacteria. *Drugs*. 1999;58:19–22.
84. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371:1577–1587.
85. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
86. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016;374:124–134.
87. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect Dis*. 2013;13:27–35.
88. García MT, Pelaz C, Giménez MJ, et al. In vitro activities of gemifloxacin versus five quinolones and two macrolides against 271 Spanish isolates of *Legionella pneumophila:* influence of charcoal on susceptibility test results. *Antimicrob Agents Chemother*. 2000;44:2176–2178.
89. Howard BM, Pinney RJ, Smith JT. 4-quinolone bactericidal mechanisms. *Arzneimittelforschung*. 1993;43:1125–1129.
90. Lister PD, Wolter DJ, Wickman PA, et al. Levofloxacin/imipenem prevents the emergence of high-level resistance among *Pseudomonas aeruginosa* strains already lacking susceptibility to one or both drugs. *J Antimicrob Chemother*. 2006;57:999–1003.
91. Kanellakopoulou K, Sarafis P, Galani I, et al. In vitro synergism of β-lactams with ciprofloxacin and moxifloxacin against genetically distinct multidrug-resistant isolates of *Pseudomonas aeruginosa*. *Int J Antimicrob Agents*. 2008;32:33–39.
92. Louie A, Liu W, VanGuilder M, et al. Combination treatment with meropenem plus levofloxacin is synergistic against pseudomonas aeruginosa infection in a murine model of pneumonia. *J Infect Dis*. 2015;211:1326–1333.
93. Hackbarth CJ, Chambers HF, Sande MA. Serum bactericidal activity of rifampin in combination with other antimicrobial agents against *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 1986;29:611–613.
94. Balasubramanian V, Solapure S, Gaonkar S, et al. Effect of coadministration of moxifloxacin and rifampin on *Mycobacterium tuberculosis* in a murine aerosol infection model. *Antimicrob Agents Chemother*. 2012;56:3054–3057.
95. Dudley MN. Pharmacokinetics of fluoroquinolones. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:115–132.
96. Lode H, Hoffken G, Boeckk M, et al. Quinolone pharmacokinetics and metabolism. *J Antimicrob Chemother*. 1990;26(supplB):41–49.
97. Sorgel F, Kinzig M. Pharmacokinetics of gyrase inhibitors, Part 1: basic chemistry and gastrointestinal disposition. *Am J Med*. 1993;94:44S–55S.
98. Staib AH, Beermann D, Harder S, et al. Absorption differences of ciprofloxacin along the human gastrointestinal tract determined using a remote-control drug delivery device (HF-capsule). *Am J Med*. 1989;87:66S–69S.
99. Healy DP, Brodbeck MC, Clendening CE. Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother*. 1996;40:6–10.
100. Yuk JH, Nightingale CH, Sweeney KR, et al. Relative bioavailability in healthy volunteers of ciprofloxacin administered through a nasogastric tube with and without enteral feeding. *Antimicrob Agents Chemother*. 1989;33:1118–1120.
101. Tamai I, Yamashita J, Kido Y, et al. Limited distribution of new quinolone antibacterial agents into brain caused by multiple efflux transporters at the blood-brain barrier. *J Pharmacol Exp Ther*. 2000;295:146–152.
102. Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev*. 2010;23:858–883.
103. Alffenaar JW, van Altena R, Bökkerink HJ, et al. Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. *Clin Infect Dis*. 2009;49:1080–1082.
104. Thwaites GE, Bhavnani SM, Chau TT, et al. Randomized pharmacokinetic and pharmacodynamic comparison of fluoroquinolones for tuberculous meningitis. *Antimicrob Agents Chemother*. 2011;55:3244–3253.
105. Montay G, Gaillot J. Pharmacokinetics of fluoroquinolones in hepatic failure. *J Antimicrob Chemother*. 1990;26(supplB):61–67.
106. Giamarellou H, Kolokythas E, Petrikkos G, et al. Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med*. 1989;87:49S–51S.
107. Sorgel F, Kinzig M. Pharmacokinetics of gyrase inhibitors, Part 2: renal and hepatic elimination pathways and drug interactions. *Am J Med*. 1993;94:56S–69S.
108. Stass H, Bührmann S, Mitchell A, et al. The influence of continuous venovenous haemodialysis on the pharmacokinetics of multiple oral moxifloxacin admininstration to patients with severe renal dysfunction. *Br J Clin Pharmacol*. 2007;64:745–749.
109. Fillastre JP, Leroy A, Moulin B, et al. Pharmacokinetics of quinolones in renal insufficiency. *J Antimicrob Chemother*. 1990;26(suppl 8):51–60.
110. Malone RS, Fish DN, Abraham E, et al. Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother*. 2001;45:2949–2954.
111. Traunmuller F, Thalhammer-Scherrer R, Locker G, et al. Single-dose pharmacokinetics of levofloxacin during continuous veno-venous haemofiltration in critically ill patients. *J Antimicrob Chemother*. 2001;47:229–231.
112. Fuhrmann V, Schenk P, Jaeger W, et al. Pharmacokinetics of moxifloxacin in patients undergoing continuous venovenous haemodiafiltration. *J Antimicrob Chemother*. 2004;54:780–784.
113. Hooper DC. New uses for new and old quinolones and the challenge of resistance. *Clin Infect Dis*. 2000;30:243–254.
114. Radandt JM, Marchbanks CR, Dudley MN. Interactions of fluoroquinolones with other drugs: mechanisms, variability, clinical significance, and management. *Clin Infect Dis*. 1992;14:272–284.
115. Qaqish R, Polk RE. Drug-drug interactions. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:133–146.
116. Polk RE, Healy DP, Sahai J, et al. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. *Antimicrob Agents Chemother*. 1989;33:1841–1844.
117. Fuhr U, Strobl G, Manaut F, et al. Quinolone antibacterial agents: relationship between structure and in vitro inhibition of the human cytochrome. *Mol Pharmacol*. 1993;43:P450 isoform CYP1A2.
118. Schwartz J, Jauregui L, Lettieri J, et al. Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. *Antimicrob Agents Chemother*. 1988;32:75–77.
119. Robson RA. The effects of quinolones on xanthine pharmacokinetics. *Am J Med*. 1992;92:22S–25S.
120. Kim MK, Nightingale C, Nicolau D. Influence of sex on the pharmacokinetic interaction of fleroxacin and ciprofloxacin with caffeine. *Clin Pharmacokinet*. 2003;42:985–986.
121. Granfors MT, Backman JT, Neuvonen M, et al. Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1a2-mediated presystemic metabolism. *Clin Pharmacol Ther*. 2004;76:598–606.
122. Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. *Eur J Clin Pharmacol*. 2000;56:585–589.
123. Weiner M, Burman W, Luo CC, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother*. 2007;51:2861–2866.
124. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis*. 2007;45:1001–1007.
125. Israel DS, Stotka J, Rock W, et al. Effect of ciprofloxacin on the pharmacokinetics and pharmacodynamics of warfarin. *Clin Infect Dis*. 1996;22:251–256.
126. Carroll DN, Carroll DG. Interactions between warfarin and three commonly prescribed fluoroquinolones. *Ann Pharmacother*. 2008;42:680–685.
127. Hori S, Shimada J, Saito A, et al. Comparison of the inhibitory effect of new quinolones on gamma-aminobutyric acid receptor binding in the presence of antiinflammatory drugs. *Rev Infect Dis*. 1989;11:S1397–S1398.
128. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. *Clin Infect Dis*. 2009;49:1–45.
129. Norrby SR. Central nervous system toxicity. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:461–465.

129a. Wolfson JS, Hooper DC. Treatment of genitourinary tract infections with fluoroquinolones: activity in vitro, pharmacokinetics, and clinical efficacy in urinary tract infections and prostatitis. *Antimicrob Agents Chemother*. 1989;33:1655–1661.

129b. Gupta K, Naber K, Stamm W. Treatment of urinary tract infections. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:159–170.

129c. Rafalsky V, Andreeva I, Rjabkova E. Quinolones for uncomplicated acute cystitis in women. *Cochrane Database Syst Rev*. 2006;(3):CD003597.

129d. Arredondo JL, Figueroa-Damian R, Rosas A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. *J Antimicrob Chemother*. 2004;54:840–843.

129e. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *N Engl J Med*. 1991;324:384–394.

129f. Iravani A, Klimberg I, Briefer C, et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother*. 1999;43:67–75.

129g. Hooton TM, Scholes D, Gupta K, et al. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. *JAMA*. 2005;293:949–955.

129h. Henry DC Jr, Bettis RB, Riffer E, et al. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. *Clin Ther*. 2002;24:2088–2104.

129i. Fourcroy JL, Berner B, Chiang YK, et al. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. *Antimicrob Agents Chemother*. 2005;49:4137–4143.

129j. Raz R, Rottensterich E, Hefter H, et al. Single-dose ciprofloxacin in the treatment of uncomplicated urinary tract infection in women. *Eur J Clin Microbiol Infect Dis*. 1989;8:1040–1042.

129k. Pfau A, Sacks TG. Single dose quinolone treatment in acute uncomplicated urinary tract infection in women. *J Urol*. 1993;149:532–534.

129l. Saginur R, Nicolle LE. Single-dose compared with 3-day norfloxacin treatment of uncomplicated urinary tract infection in women. Canadian Infectious Diseases Society

Clinical Trials Study Group. *Arch Intern Med*. 1992;152:1233–1237.

129m. The Urinary Tract Infection Study Group. Coordinated multicenter study of norfloxacin versus trimethoprim-sulfamethoxazole of symptomatic urinary tract infections. *J Infect Dis*. 1987;155:170–177.

129n. Raz R, Rottensterich E, Leshem Y, et al. Double-blind study comparing 3-day regimens of cefixime and ofloxacin in treatment of uncomplicated urinary tract infections in women. *Antimicrob Agents Chemother*. 1994;38:1176–1177.

129o. Mombelli G, Pezzoli R, Pinoja-Lutz G, et al. Oral vs intravenous ciprofloxacin in the initial empirical management of severe pyelonephritis or complicated urinary tract infections: a prospective randomized clinical trial. *Arch Intern Med*. 1999;159:53–58.

129p. Richard GA, Klimberg IN, Fowler CL, et al. Levofloxacin versus ciprofloxacin versus lomefloxacin in acute pyelonephritis. *Urology*. 1998;52:51–55.

129q. Peterson J, Kaul S, Khashab M, et al. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. *Urology*. 2008;71:17–22.

130. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious diseases society of America and the European society for microbiology and infectious diseases. *Clin Infect Dis*. 2011;52:e103–e120.

131. Gagliotti C, Buttazzi R, Sforza S, et al. Resistance to fluoroquinolones and treatment failure/short-term relapse of community-acquired urinary tract infections caused by *Escherichia coli*. *J Infect*. 2008;57:179–184.

132. Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis*. 2002;34:1165–1169.

133. Manges AR, Johnson JR, Foxman B, et al. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. *N Engl J Med*. 2001;345:1007–1013.

134. Banerjee R, Johnson JR. A new clone sweeps clean: the enigmatic emergence of escherichia coli sequence type 131. *Antimicrob Agents Chemother*. 2014;58:4997–5004.

135. Jones GL, Warren RE, Skidmore SJ, et al. Prevalence and distribution of plasmid-mediated quinolone resistance genes in clinical isolates of escherichia coli lacking extended-spectrum β-lactamases. *J Antimicrob Chemother*. 2008;62:1245–1251.

136. Huntington JA, Sakoulas G, Umeh O, et al. Efficacy of ceftolozane/tazobactam versus levofloxacin in the treatment of complicated urinary tract infections (cUTIs) caused by levofloxacin-resistant pathogens: results from the ASPECT-cUTI trial. *J Antimicrob Chemother*. 2016;71:2014–2021.

137. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. *Lancet*. 2012;380:484–490.

138. van Nieuwkoop C, van der Starre WE, Stalenhoef JE, et al. Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women. *BMC Med*. 2017;15:70.

139. Johnson JR, Porter S, Thures P, et al. The pandemic *H*30 subclone of sequence type 131 (ST131) as the leading casue of multidrug-resistant *Escherichia coli* infections in the United States (2011-2012). *Open Forum Infect Dis*. 2017;4:doi:10.1093/ofid/ofx089.

140. Raz R, Boger S. Long-term prophylaxis with norfloxacin versus nitrofurantoin in women with recurrent urinary tract infection. *Antimicrob Agents Chemother*. 1991;35:1241–1242.

141. Pfau A, Sacks TG. Effective postcoital quinolone prophylaxis of recurrent urinary tract infections in women. *J Urol*. 1994;152:136–138.

142. Mody L. Juthani-mehta M. Urinary tract infections in older women: a clinical review. *JAMA*. 2014;311:844–854.

143. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *N Engl J Med*. 1991;324:384–394.

144. Fang GD, Brennen C, Wagener M, et al. Use of ciprofloxacin versus use of aminoglycosides for therapy of complicated urinary tract infection: prospective, randomized clinical and pharmacokinetic study. *Antimicrob Agents Chemother*. 1991;35:1849–1855.

145. Schaeffer AJ, Nicolle LE. Clinical practice. Urinary tract infections in older men. *N Engl J Med*. 2016;374:562–571.

146. Dow G, Rao P, Harding G, et al. A prospective, randomized trial of 3 or 14 days of ciprofloxacin treatment for acute urinary tract infection in patients with spinal cord injury. *Clin Infect Dis*. 2004;39:658–664.

147. Peng MY. Randomized, double-blind, comparative study of levofloxacin and ofloxacin in the treatment of complicated urinary tract infections. *J Microbiol Immunol Infect*. 1999;32:33–39.

148. Pisani E, Bartoletti R, Trinchieri A, et al. Lomefloxacin versus ciprofloxacin in the treatment of complicated urinary tract infections: a multicenter study. *J Chemother*. 1996;8:210–213.

149. Nakano M, Yasuda M, Yokoi S, et al. In vivo selection of *Pseudomonas aeruginosa* with decreased susceptibilities to fluoroquinolones during fluoroquinolone treatment of urinary tract infection. *Urology*. 2001;58:125–128.

150. Biering-Sørensen F, Høiby N, Nordenbo A, et al. Ciprofloxacin as prophylaxis for urinary tract infection: prospective, randomized, cross-over, placebo controlled study in patients with spinal cord lesion. *J Urol*. 1994;151:105–108.

151. Christiano AP, Hollowell CMP, Kim H, et al. Double-blind randomized comparison of single-dose ciprofloxacin versus intravenous cefazolin in patients undergoing outpatient endourologic surgery. *Urology*. 2000;55:182–185.

152. Klimberg IW, Malek GH, Cox CE, et al. Single-dose oral ciprofloxacin compared with cefotaxime and placebo for prophylaxis during transurethral surgery. *J Antimicrob Chemother*. 1999;43:77–84.

153. Isen K, Kupeli B, Sinik Z, et al. Antibiotic prophylaxis for transrectal biopsy of the prostate: a prospective randomized study of the prophylactic use of single dose oral fluoroquinolone versus trimethoprim-sulfamethoxazole. *Int Urol Nephrol*. 1999;31:491–495.

154. Wagenlehner FM, Wagenlehner C, Schinzel S, et al. Prospective, randomized, multicentric, open, comparative study on the efficacy of a prophylactic single dose of 500 mg levofloxacin versus 1920 mg trimethoprim/sulfamethoxazole versus a control group in patients undergoing TUR of the prostate. *Eur Urol*. 2005;47:549–556.

155. Berry A, Barratt A. Prophylatic antibiotic use in transurethral prostatic resection: a meta-analysis. *J Urol*. 2002;167:571–577.

156. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. *BJU Int*. 2000;85:682–685.

157. Kapoor DA, Klimberg IW, Malek GH, et al. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. *Urology*. 1998;52:552–558.

158. Bootsma AM, Laguna Pes MP, Geerlings SE, et al. Antibiotic prophylaxis in urologic procedures: a systematic review. *Eur Urol*. 2008;54:1270–1286.

159. Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol*. 2008;179:1379–1390.

160. Moyses NM, Costa RS, Reis MA, et al. Use of ciprofloxacin as a prophylactic agent in urinary tract infections in renal transplant recipients. *Clin Transplant*. 1997;11:446–452.

161. Sabbaj J, Hoagland VL, Cook T. Norfloxacin versus co-trimoxazole in the treatment of recurring urinary tract infections in men. *Scand J Infect Dis*. 1986;48:48–53.

162. Naber KG, Weidner W. Chronic prostatitis: an infectious disease? *J Antimicrob Chemother*. 2000;46:157–161.

163. Naber KG, Roscher K, Botto H, et al. Oral levofloxacin 500 mg once daily in the treatment of chronic bacterial prostatitis. *Int J Antimicrob Agents*. 2008;32:145–153.

164. Giannarini G, Mogorovich A, Valent F, et al. Prulifloxacin versus levofloxacin in the treatment of chronic bacterial prostatitis: a prospective, randomized, double-blind trial. *J Chemother*. 2007;19:304–308.

165. Schaeffer AJ, Darras FS. The efficacy of norfloxacin in the treatment of chronic bacterial prostatitis refractory to trimethoprim-sulfamethoxazole and/or carbenicillin. *J Urol*. 1990;144:690–693.

166. Williamson DA, Barrett LK, Rogers BA, et al. Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant *Escherichia coli*. *Clin Infect Dis*. 2013;57:267–274.

167. Liss MA, Johnson JR, Porter SB, et al. Clinical and microbiological determinants of infection after transrectal prostate biopsy. *Clin Infect Dis*. 2015;60:979–987.

168. Liss MA, Kim W, Moskowitz D, et al. Comparative effectiveness of targeted vs empirical antibiotic prophylaxis to prevent sepsis from transrectal prostate biopsy: A retrospective analysis. *J Urol*. 2015;194:397–402.

169. Marino K, Parlee A, Orlando R, et al. Comparative effectiveness of single versus combination antibiotic prophylaxis for infections after transrectal prostate biopsy. *Antimicrob Agents Chemother*. 2015;59:7273–7275.

170. Chamberland RR. Cutting to the core of the issue: emerging strategies to reduce prostate biopsy-related infections. *J Clin Microbiol*. 2016;54:2431–2435.

171. Eschenbach D. Treatment of pelvic inflammatory disease. *Clin Infect Dis*. 2007;44:961–963.

172. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. *Clin Infect Dis*. 2007;44:S84–S101.

173. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guideline, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2007;56:332–336.

174. Peeling RW, Ronald AR. Use of quinolones for treatment of sexually transmitted diseases. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:171–192.

175. Hooper DC, Wolfson JS. Treatment of genitourinary tract infections with fluoroquinolones: clinical efficacy in genital infections and adverse effects. *Antimicrob Agents Chemother*. 1989;33:1662–1667.

176. Thorpe EM, Schwebke JR, Hook EW, et al. Comparison of single-dose cefuroxime axetil with ciprofloxacin in treatment of uncomplicated gonorrhea caused by penicillinase-producing and non-penicillinase-producing *Neisseria gonorrhoeae* strains. *Antimicrob Agents Chemother*. 1996;40:2775–2780.

177. Lutz FB Jr. Single-dose efficacy of ofloxacin in uncomplicated gonorrhea. *Am J Med*. 1989;87:69S–74S.

178. Boslego JW, Hicks CB, Greenup R, et al. A prospective randomized trial of ofloxacin vs. doxycycline in the treatment of uncomplicated male urethritis. *Sex Transm Dis*. 1988;15:186–191.

179. Hooton TM, Batteiger BE, Judson FN, et al. Ofloxacin versus doxycycline for treatment of cervical infection with *Chlamydia trachomatis*. *Antimicrob Agents Chemother*. 1992;36:1144–1146.

180. Kitchen VS, Donegan C, Ward H, et al. Comparison of ofloxacin with doxycycline in the treatment of non-gonococcal urethritis and cervical chlamydial infection. *J Antimicrob Chemother*. 1990;26(supplD):99–105.

181. Mikamo H, Sato Y, Hayasaki Y, et al. Adequate levofloxacin treatment schedules for uterine cervicitis caused by *Chlamydia trachomatis*. *Chemotherapy*. 2000;46:150–152.

182. Geisler WM. Diagnosis and management of uncomplicated *Chlamydia trachomatis* infections in adolescents and adults: summary of evidence reviewed for the 2015 centers for disease control and prevention sexually transmitted diseases treatment guidelines. *Clin Infect Dis*. 2015;61(suppl 8):S774–S784.

183. Wendel GDJ, Cox SM, Bawdon RE, et al. A randomized trial of ofloxacin versus cefoxitin and doxycycline in the outpatient treatment of acute salpingitis. *Am J Obstet Gynecol*. 1991;164:1390–1396.

184. Crombleholme WR, Schachter J, Ohm-Smith M, et al. Efficacy of single-agent therapy for the treatment of acute pelvic inflammatory disease with ciprofloxacin. *Am J Med*. 1989;87:142S–147S.

185. Martens MG, Gordon S, Yarborough DR, et al. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. *South Med J*. 1993;86:604–610.

186. Arredondo JL, Diaz V, Gaitan H, et al. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to-moderate pelvic inflammatory disease in outpatients. *Clin Infect Dis*. 1997;24:170–178.

187. Judlin P, Liao Q, Liu Z, et al. Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. *BJOG*. 2010;117:1475–1484.

188. Naamara W, Plummer FA, Greenblatt RM, et al. Treatment of chancroid with ciprofloxacin. A prospective, randomized clinical trial. *Am J Med*. 1987;82:317–320.

189. Malonza IM, Tyndall MW, Ndinya-Achola JO, et al. A randomized, double-blind, placebo-controlled trial of single-dose ciprofloxacin versus erythromycin for the treatment of chancroid in nairobi, Kenya. *J Infect Dis*. 1999;180:1886–1893.

190. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep*. 2006;55(RR–11):1–94.

191. Covino JM, Black JR, Cummings M, et al. Comparative evaluation of ofloxacin and metronidazole in the treatment of bacterial vaginosis. *Sex Transm Dis*. 1993;20:262–264.

192. Bennish ML. Treatment and prophylaxis of gastroenteritis. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:193–216.
193. Wiström J, Jertborn M, Hedstrom SA, et al. Short-term self-treatment of travellers' diarrhoea with norfloxacin: a placebo-controlled study. *J Antimicrob Chemother*. 1989;23:905–913.
194. Ericsson CD, Johnson PC, DuPont HL, et al. Ciprofloxacin or trimethoprim-sulfamethoxazole as initial therapy for travelers' diarrhea. A placebo-controlled, randomized trial. *Ann Intern Med*. 1987;106:216–220.
195. Gomi H, Jiang ZD, Adachi JA, et al. In vitro antimicrobial susceptibility testing of bacterial enteropathogens causing traveler's diarrhea in four geographic regions. *Antimicrob Agents Chemother*. 2001;45:212–216.
196. Petruccelli BP, Murphy GS, Sanchez JL, et al. Treatment of travelers' diarrhea with ciprofloxacin and loperamide. *J Infect Dis*. 1992;165:557–560.
197. Salam I, Katelaris P, Leigh-Smith S, et al. Randomised trial of single-dose ciprofloxacin for travellers' diarrhoea. *Lancet*. 1994;344:1537–1539.
198. Ericsson CD, DuPont HL, Matthewson JJ. Single dose ofloxacin plus loperamide compared with single dose or three days of ofloxacin in the treatment of traveler's diarrhea. *J Travel Med*. 1997;4:3–7.
199. Sanders JW, Frenck RW, Putnam SD, et al. Azithromycin and loperamide are comparable to levofloxacin and loperamide for the treatment of traveler's diarrhea in United States military personnel in Turkey. *Clin Infect Dis*. 2007;45:294–301.
200. DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. *N Engl J Med*. 1993;328:1821–1827.
201. Heck JE, Staneck JL, Cohen MB, et al. Prevention of travelers' diarrhea: ciprofloxacin versus trimethoprim/sulfamethoxazole in adult volunteers working in latin America and the caribbean. *J Travel Med*. 1994;1:136–142.
202. Mattila L, Peltola H, Siitonen A, et al. Short-term treatment of traveler's diarrhea with norfloxacin: a double-blind, placebo-controlled study during two seasons. *Clin Infect Dis*. 1993;17:779–782.
203. Khan WA, Seas C, Dhar U, et al. Treatment of shigellosis: V. Comparison of azithromycin and ciprofloxacin. A double-blind, randomized, controlled trial. *Ann Intern Med*. 1997;126:697–703.
204. Murphy GS, Bodhidatta L, Echeverria P, et al. Ciprofloxacin and loperamide in the treatment of bacillary dysentery. *Ann Intern Med*. 1993;118:582–586.
205. Bennish ML, Salam MA, Khan WA, et al. Treatment of shigellosis: III. Comparison of one- or two-dose ciprofloxacin with standard 5-day therapy. A randomized, blinded trial. *Ann Intern Med*. 1992;117:727–734.
206. Gu B, Cao Y, Pan S, et al. Comparison of the prevalence and changing resistance to nalidixic acid and ciprofloxacin of *Shigella* between Europe-America and Asia-Africa from 1998 to 2009. *Int J Antimicrob Agents*. 2012;40:9–17.
207. Pichler HE, Diridl G, Wolf D. Ciprofloxacin in the treatment of acute bacterial diarrhea: a double blind study. *Eur J Clin Microbiol*. 1986;5:241–243.
208. Wiström J, Jertborn M, Ekwall E, et al. Empiric treatment of acute diarrheal disease with norfloxacin. A randomized, placebo-controlled study. Swedish study group. *Ann Intern Med*. 1992;117:202–208.
209. Sanchez C, Garcia-Restoy E, Garau J, et al. Ciprofloxacin and trimethoprim-sulfamethoxazole versus placebo in acute uncomplicated *Salmonella* gastroenteritis: a double-blind trial. *J Infect Dis*. 1993;168:1304–1307.
210. Neill MA, Opal SM, Heelan J, et al. Failure of ciprofloxacin to eradicate convalescent fecal excretion after acute salmonellosis: experience during an outbreak in health care workers. *Ann Intern Med*. 1991;114:195–199.
211. Dryden MS, Gabb RJ, Wright SK. Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin. *Clin Infect Dis*. 1996;22:1019–1025.
212. Hung CC, Hsieh SM, Hsiao CF, et al. Risk of recurrent non-typhoidal *Salmonella* bacteraemia after early discontinuation of ciprofloxacin as secondary prophylaxis in AIDS patients in the era of highly active antiretroviral therapy. *AIDS*. 2001;15:645–647.
213. Pichler HE, Diridl G, Stickler K, et al. Clinical efficacy of ciprofloxacin compared with placebo in bacterial diarrhea. *Am J Med*. 1987;82:329–332.
214. Goodman LJ, Trenholme GM, Kaplan RL, et al. Empiric antimicrobial therapy of domestically acquired acute diarrhea in urban adults. *Arch Intern Med*. 1990;150:541–546.
214a. Smith KE, Besser JM, Hedberg CW, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998. *N Engl J Med*. 1999;340:1525–1532.
215. Tribble DR, Sanders JW, Pang LW, et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. *Clin Infect Dis*. 2007;44:338–346.
216. Bhattacharya SK, Bhattacharya MK, Dutta P, et al. Double-blind, randomized, controlled clinical trial of norfloxacin for cholera. *Antimicrob Agents Chemother*. 1990;34:939–940.
217. Dutta D, Bhattacharya SK, Bhattacharya MK, et al. Efficacy of norfloxacin and doxycycline for treatment of *Vibrio cholerae* O139 infection. *J Antimicrob Chemother*. 1996;37:575–581.
218. Khan WA, Bennish ML, Seas C, et al. Randomised controlled comparison of single-dose ciprofloxacin and doxycycline for cholera caused by *Vibrio cholerae* 01 or 0139. *Lancet*. 1996;348:296–300.
219. Usubutun S, Agalar C, Diri C, et al. Single dose ciprofloxacin in cholera. *Eur J Emerg Med*. 1997;4:145–149.
220. Saha D, Khan WA, Karim MM, et al. Single-dose ciprofloxacin versus 12-dose erythromycin for childhood cholera: a randomised controlled trial. *Lancet*. 2005;366:1085–1093.
221. Saha D, Karim MM, Khan WA, et al. Single-dose azithromycin for the treatment of cholera in adults. *N Engl J Med*. 2006;354:2452–2462.
222. Rashed SM, Hasan NA, Alam M, et al. *Vibrio cholerae* O1 with reduced susceptibility to ciprofloxacin and azithromycin isolated from a rural coastal area of Bangladesh. *Front Microbiol*. 2017;8:252.
223. Parry CM, Hien TT, Dougan G, et al. Typhoid fever. *N Engl J Med*. 2002;347:1770–1782.
224. Cooke FJ, Day M, Wain J, et al. Cases of typhoid fever imported into England, Scotland and Wales (2000-2003). *Trans R Soc Trop Med Hyg*. 2007;101:398–404.
225. Wain J, Hoa NT, Chinh NT, et al. Quinolone-resistant *Salmonella typhi* in Viet Nam: molecular basis of resistance and clinical response to treatment. *Clin Infect Dis*. 1997;25:1404–1410.
226. Parry CM, Ho VA, Phuong LT, et al. Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrob Agents Chemother*. 2007;51:819–825.
227. Hume S, Schulz T, Vinton P, et al. Increasing rates and clinical consequences of nalidixic acid-resistant isolates causing enteric fever in returned travelers: an 18-year experience. *Eur J Clin Microbiol Infect Dis*. 2009;28:963–970.
228. Lynch MF, Blanton EM, Bulens S, et al. Typhoid fever in the United States, 1999-2006. *JAMA*. 2009;302:859–865.
229. Koirala S, Basnyat B, Arjyal A, et al. Gatifloxacin versus ofloxacin for the treatment of uncomplicated enteric fever in Nepal: an open-label, randomized, controlled trial. *PLoS Negl Trop Dis*. 2013;7:e2523.
230. Arjyal A, Basnyat B, Nhan HT, et al. Gatifloxacin versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial. *Lancet Infect Dis*. 2016;16:535–545.
231. Gotuzzo E, Guerra JG, Benavente L, et al. Use of norfloxacin to treat chronic typhoid carriers. *J Infect Dis*. 1988;157:1221–1225.
232. Ferreccio C, Morris JGJ, Valdivieso C, et al. Efficacy of ciprofloxacin in the treatment of chronic typhoid carriers. *J Infect Dis*. 1988;157:1235–1239.
233. Gisbert JP, Bermejo F, Castro-Fernandez M, et al. Second-line rescue therapy with levofloxacin after *H. pylori* treatment failure: a Spanish multicenter study of 300 patients. *Am J Gastroenterol*. 2008;103:71–76.
234. Miehlke S, Schneider-Brachert W, Kirsch C, et al. One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter*. 2008;13:69–74.
235. Gisbert JP, Fernandez-Bermejo M, Molina-Infante J, et al. First-line triple therapy with levofloxacin for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2007;26:495–500.
236. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther*. 2006;23:35–44.
237. Nista EC, Candelli M, Zocco MA, et al. Levofloxacin-based triple therapy in first-line treatment for *Helicobacter pylori* eradication. *Am J Gastroenterol*. 2006;101:1985–1990.
238. Matsumoto Y, Miki I, Aoyama N, et al. Levofloxacin-versus metronidazole-based rescue therapy for *H. pylori* infection in Japan. *Dig Liver Dis*. 2005;37:821–825.
239. Li Y, Huang X, Yao L, et al. Advantages of moxifloxacin and levofloxacin-based triple therapy for second-line treatments of persistent *Helicobacter pylori* infection: a metaanalysis. *Wein Klin Wochenschr*. 2010;122:413–422.
240. Liao J, Zheng Q, Liang X, et al. Effect of fluoroquinolone resistance on 14-day levofloxacin triple and triple plus bismuth quadruple therapy. *Helicobacter*. 2013;18:373–377.
241. Fallone CA, Chiba N, van Zanten SV, et al. The toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology*. 2016;151:51–69. e14.
242. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut*. 2015;64:1353–1367.
243. Chrysanthopoulos CJ, Skoutelis AT, Starakis JC, et al. Use of ciprofloxacin in biliary sepsis. *Infection*. 1988;16:249–250.
244. Sung JJ, Sollano JD, Lai CW, et al. Long-term ciprofloxacin treatment for the prevention of biliary stent blockage: a prospective randomized study. *Am J Gastroenterol*. 1999;94:3197–3201.
245. Chan G, Barkun J, Barkun AN, et al. The role of ciprofloxacin in prolonging polyethylene biliary stent patency: a multicenter, double-blinded effectiveness study. *J Gastrointest Surg*. 2005;9:481–488.
246. Solomkin JS, Reinhart HH, Dellinger EP, et al. Results of a randomized trial comparing sequential intravenous oral treatment with ciprofloxacin plus metronidazole to imipenem cilastatin for intra-abdominal infections. *Ann Surg*. 1996;223:303–315.
247. Solomkin JS. Treatment of intra-abdominal infections. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:217–225.
248. Cohn SM, Lipsett PA, Buchman TG, et al. Comparison of intravenous/oral ciprofloxacin plus metronidazole versus piperacillin/tazobactam in the treatment of complicated intra-abdominal infections. *Ann Surg*. 2000;232:254–262.
249. Wacha H, Warren B, Bassaris H, et al. Comparison of sequential intravenous/oral ciprofloxacin plus metronidazole with intravenous ceftriaxone plus metronidazole for treatment of complicated intra-abdominal infections. *Surg Infect (Larchmt)*. 2006;7:341–354.
250. Malangoni MA, Song J, Herrington J, et al. Randomized controlled trial of moxifloxacin compared with piperacillin-tazobactam and amoxicillin-clavulanate for the treatment of complicated intra-abdominal infections. *Ann Surg*. 2006;244:204–211.
251. Solomkin J, Zhao YP, Ma EL, et al. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intraabdominal infections. *Int J Antimicrob Agents*. 2009;34:439–445.
252. Goldstein EJ, Solomkin JS, Citron DM, et al. Clinical efficacy and correlation of clinical outcomes with in vitro susceptibility for anaerobic bacteria in patients with complicated intraabdominal infections treated with moxifloxacin. *Clin Infect Dis*. 2011;53:1074–1080.
253. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guideline by the surgical infection society and the infectious diseases society of America. *Clin Infect Dis*. 2010;50:133–164.
254. Friedland JS, Iveson TJ, Fraise AP, et al. A comparison between intraperitoneal ciprofloxacin and intraperitoneal vancomycin and gentamicin in the treatment of peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD). *J Antimicrob Chemother*. 1990;26:77–81.
255. de Fijter CW, ter Wee PM, Oe LP, et al. Intraperitoneal ciprofloxacin and rifampicin versus cephradine as initial treatment of (C)APD-related peritonitis: a prospective randomized multicenter comparison (CIPPER trial). *Perit Dial Int*. 2001;21:480–486.
256. Cheng IK, Fang GX, Chau PY, et al. A randomized prospective comparison of oral levofloxacin plus intraperitoneal (IP) vancomycin and IP netromycin plus IP vancomycin as primary treatment of peritonitis complicating CAPD. *Perit Dial Int*. 1998;18:371–375.
257. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36:481–508.
258. Chavez-Tapia NC, Soares-Weiser K, Brezis M, et al. Antibiotics for spontaneous bacterial peritonitis in cirrhotic patients. *Cochrane Database Syst Rev*. 2009;(21):CD002232.
259. Gines P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology*. 1990;12:716–724.
260. Terg R, Fassio E, Guevara M, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis:

a randomized, placebo-controlled study. *J Hepatol*. 2008;48:774–779.

261. Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology*. 2007;133:818–824.
262. Grange JD, Roulot D, Pelletier G, et al. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. *J Hepatol*. 1998;29:430–436.
263. Novella M, Solà R, Soriano G, et al. Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. *Hepatology*. 1997;25:532–536.
264. Rolachon A, Cordier L, Bacq Y, et al. Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. *Hepatology*. 1995;22:1171–1174.
265. Dupeyron C, Mangeney N, Sedrati L, et al. Rapid emergence of quinolone resistance in cirrhotic patients treated with norfloxacin to prevent spontaneous bacterial peritonitis. *Antimicrob Agents Chemother*. 1994;38:340–344.
266. Cereto F, Molina I, Gonzalez A, et al. Role of immunosuppression in the development of quinolone-resistant *Escherichia coli* spontaneous bacterial peritonitis and in the mortality of E. coli spontaneous bacterial peritonitis. *Aliment Pharmacol Ther*. 2003;17:695–701.
267. Soares-Weiser K, Brezis M, Tur-Kaspa R, et al. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. *Cochrane Database Syst Rev*. 2002;(2):CD002907.
268. Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology*. 2006;131:1049–1056.
269. Ball P, Mandell L. Treatment of community-acquired respiratory tract infections. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:227–243.
270. Anzueto A, Miravitlles M. Short-course fluoroquinolone therapy in exacerbations of chronic bronchitis and COPD. *Respir Med*. 2010;104:1396–1403.
271. DeAbate CA, Russell M, McElvaine P, et al. Safety and efficacy of oral levofloxacin versus cefuroxime axetil in acute bacterial exacerbation of chronic bronchitis. *Respir Care*. 1997;42:206–213.
272. Shah PM, Maesen FP, Dolmann A, et al. Levofloxacin versus cefuroxime axetil in the treatment of acute exacerbation of chronic bronchitis: results of a randomized, double-blind study. *J Antimicrob Chemother*. 1999;43:529–539.
273. Davies BI, Maesen FPV. Clinical effectiveness of levofloxacin in patients with acute purulent exacerbations of chronic bronchitis: the relationship with in vitro activity. *J Antimicrob Chemother*. 1999;43:83–90.
274. Wilson R, Kubin R, Ballin I, et al. Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemother*. 1999;44:501–513.
275. Chodosh S, DeAbate CA, Haverstock D, et al. Short-course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis. The bronchitis study group. *Respir Med*. 2000;94:18–27.
276. DeAbate CA, Mathew CP, Warner JH, et al. The safety and efficacy of short course (5-day) moxifloxacin vs. azithromycin in the treatment of patients with acute exacerbation of chronic bronchitis. *Respir Med*. 2000;94:1029–1037.
277. Zervos M, Martinez FJ, Amsden GW, et al. Efficacy and safety of 3-day azithromycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis. *Int J Antimicrob Agents*. 2007;29:56–61.
278. Urueta-Robledo J, Ariza H, Jardim JR, et al. Moxifloxacin versus levofloxacin against acute exacerbations of chronic bronchitis: the latin American cohort. *Respir Med*. 2006;100:1504–1511.
279. Rhee CK, Chang JH, Choi EG, et al. Zabofloxacin versus moxifloxacin in patients with COPD exacerbation: a multicenter, double-blind, double-dummy, randomized, controlled, Phase III, non-inferiority trial. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2265–2275.
280. Wilson R, Schentag JJ, Ball P, et al. A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin Ther*. 2002;24:639–652.
281. Sethi S, Fogarty C, Fulambarker A. A randomized, double-blind study comparing 5 days oral gemifloxacin with 7 days oral levofloxacin in patients with acute exacerbation of chronic bronchitis. *Respir Med*. 2004;98:697–707.
282. Wilson R, Allegra L, Huchon G, et al. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest*. 2004;125:953–964.
283. Wilson R, Langan C, Ball P, et al. Oral gemifloxacin once daily for 5 days compared with sequential therapy with i.v. ceftriaxone/oral cefuroxime (maximum of 10 days) in the treatment of hospitalized patients with acute exacerbations of chronic bronchitis. *Respir Med*. 2003;97:242–249.
284. Chodosh S, Schreurs A, Siami G, et al. Efficacy of oral ciprofloxacin vs. clarithromycin for treatment of acute bacterial exacerbations of chronic bronchitis. *Clin Infect Dis*. 1998;27:730–738.
285. Chodosh S, McCarty J, Farkas S, et al. Randomized, double-blind study of ciprofloxacin and cefuroxime axetil for treatment of acute bacterial exacerbations of chronic bronchitis. *Clin Infect Dis*. 1998;27:722–729.
286. Brill SE, Law M, El-Emir E, et al. Effects of different antibiotic classes on airway bacteria in stable COPD using culture and molecular techniques: a randomised controlled trial. *Thorax*. 2015;70:930–938.
287. Chrysanthopoulos CJ, Starakis JC, Skoutelis AT, et al. Sequential intravenous/oral therapy with ciprofloxacin in severe infection. *Am J Med*. 1989;87:225S–227S.
288. Gentry LO, Rodriguez-Gomez G, Kohler RB, et al. Parenteral followed by oral ofloxacin for nosocomial pneumonia and community-acquired pneumonia requiring hospitalization. *Am Rev Respir Dis*. 1992;145:31–35.
289. Plouffe JF, Herbert MT, File TM Jr, et al. Ofloxacin versus standard therapy in treatment of community-acquired pneumonia requiring hospitalization. *Antimicrob Agents Chemother*. 1996;40:1175–1179.
290. Sanders WE Jr, Morris JF, Alessi P, et al. Oral ofloxacin for the treatment of acute bacterial pneumonia: use of a nontraditional protocol to compare experimental therapy with "usual care" in a multicenter clinical trial. *Am J Med*. 1991;91:261–266.
291. File TM Jr, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother*. 1997;41:1965–1972.
292. Norrby SR, Petermann W, Willcox PA, et al. A comparative study of levofloxacin and ceftriaxone in the treatment of hospitalized patients with pneumonia. *Scand J Infect Dis*. 1998;30:397–404.
293. Carbon C, Ariza H, Rabie WJ, et al. Comparative study of levofloxacin and amoxycillin-clavulanic acid in adults with mild-to-moderate community-acquired pneumonia. *Clin Microbiol Infect*. 1999;5:724–732.
294. Fogarty C, Siami G, Kohler R, et al. Multicenter, open-label, randomized study to compare the safety and efficacy of levofloxacin versus ceftriaxone sodium and erythromycin followed by clarithromycin and amoxicillin-clavulanate in the treatment of serious community-acquired pneumonia in adults. *Clin Infect Dis*. 2004;38:S16–S23.
295. Bergallo C, Jasovich A, Teglia O, et al. 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.
296. Oldach D, Clark K, Schranz J, et al. Randomized, double-blind, multicenter phase 2 study comparing the efficacy and safety of oral solithromycin (CEM-101) to those of oral levofloxacin in the treatment of patients with community-acquired bacterial pneumonia. *Antimicrob Agents Chemother*. 2013;57:2526–2534.
297. Dunbar LM, Khashab MM, Kahn JB, et al. Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. *Curr Med Res Opin*. 2004;20:555–563.
298. Shorr AF, Khashab MM, Xiang JX, et al. Levofloxacin 750-mg for 5 days for the treatment of hospitalized fine risk class III/IV community-acquired pneumonia patients. *Respir Med*. 2006;100:2129–2136.
299. Fogarty C, Grossman C, Williams J, et al. Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. *Infect Med*. 1999;16:748–763.
300. Torres A, Garau J, Arvis P, et al. Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study–a randomized clinical trial. *Clin Infect Dis*. 2008;46:1499–1509.
301. Barrera CM, Mykietiuk A, Metev H, et al. Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (SOLITAIRE-ORAL). *Lancet Infect Dis*. 2016;16:421–430.
302. File TM Jr, Rewerska B, Vucinic-Mihailovic V, et al. SOLITAIRE-IV: a randomized, double-blind, multicenter study comparing the efficacy and safety of intravenous-to-oral solithromycin to intravenous-to-oral moxifloxacin for treatment of community-acquired bacterial pneumonia. *Clin Infect Dis*. 2016;63:1007–1016.
303. Petitpretz P, Arvis P, Marel M, et al. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. *Chest*. 2001;119:185–195.
304. Lode H, File TM Jr, Mandell L, et al. Oral gemifloxacin versus sequential therapy with intravenous ceftriaxone/oral cefuroxime with or without a macrolide in the treatment of patients hospitalized with community-acquired pneumonia: a randomized, open-label, multicenter study of clinical efficacy and tolerability. *Clin Ther*. 2002;24:1915–1936.
305. Léophonte P, File T, Feldman C. Gemifloxacin once daily for 7 days compared to amoxicillin/clavulanic acid thrice daily for 10 days for the treatment of community-acquired pneumonia of suspected pneumococcal origin. *Respir Med*. 2004;98:708–720.
306. File TM Jr, Mandell LA, Tillotson G, et al. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. *J Antimicrob Chemother*. 2007;60:112–120.
307. Finch R, Schürmann D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. *Antimicrob Agents Chemother*. 2002;46:1746–1754.
308. File TM Jr, Schlemmer B, Garau J, et al. Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: a randomized, double-blind comparison with trovafloxacin. *J Antimicrob Chemother*. 2001;48:67–74.
309. Anzueto A, Niederman MS, Pearle J, et al. Community-acquired pneumonia recovery in the elderly (CAPRIE): efficacy and safety of moxifloxacin therapy versus that of levofloxacin therapy. *Clin Infect Dis*. 2006;42:73–81.
310. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.
311. Kahn JB, Bahal N, Wiesinger BA, et al. Cumulative clinical trial experience with levofloxacin for patients with community-acquired pneumonia-associated pneumococcal bacteremia. *Clin Infect Dis*. 2004;38:S34–S42.
312. Portier H, Brambilla C, Garre M, et al. Moxifloxacin monotherapy compared to amoxicillin-clavulanate plus roxithromycin for nonsevere community-acquired pneumonia in adults with risk factors. *Eur J Clin Microbiol Infect Dis*. 2005;24:367–376.
313. Davidson R, Cavalcanti R, Brunton JL, et al. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N Engl J Med*. 2002;346:747–750.
314. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med*. 2015;372:1312–1323.
315. Ott SR, Allewelt M, Lorenz J, et al. Moxifloxacin vs ampicillin/sulbactam in aspiration pneumonia and primary lung abscess. *Infection*. 2008;36:23–30.
316. Mouton Y, Leroy O, Beuscart C, et al. Efficacy of intravenous ofloxacin: a French multicentre trial in 185 patients. *J Antimicrob Chemother*. 1990;26(supplD):115–121.
317. Unertl KE, Lenhart FP, Forst H, et al. Ciprofloxacin in the treatment of legionellosis in critically ill patients including those cases unresponsive to erythromycin. *Am J Med*. 1989;87:128S–131S.
318. Lipsky BA, Tack KJ, Kuo CC, et al. Ofloxacin treatment of *Chlamydia pneumoniae* (strain TWAR) lower respiratory tract infections. *Am J Med*. 1990;89:722–724.
319. Fogarty C, Grossman C, Williams J, et al. Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. *Infect Med*. 1999;16:748–763.
320. Blázquez Garrido RM, Espinosa Parra FJ, Alemany Francés L, et al. Antimicrobial chemotherapy for legionnaires disease: levofloxacin versus macrolides. *Clin Infect Dis*. 2005;40:800–806.
321. Mykietiuk A, Carratala J, Fernandez-Sabe N, et al. Clinical outcomes for hospitalized patients with *Legionella* pneumonia in the antigenuria era: the influence of levofloxacin therapy. *Clin Infect Dis*. 2005;40:794–799.
322. Edelstein PH. Antimicrobial chemotherapy for Legionnaire's disease: time for a change. *Ann Intern Med*. 1998;129:328–330.

323. Peloquin CA, Cumbo TJ, Nix DE, et al. Evaluation of intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections. Impact of plasma concentrations, organism, minimum inhibitory concentration, and clinical condition on bacterial eradication. *Arch Intern Med*. 1989;149:2269–2273.
324. Fink MP, Snydman DR, Niederman MS, et al. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. *Antimicrob Agents Chemother*. 1994;38:547–557.
325. West M, Boulanger BR, Fogarty C, et al. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. *Clin Ther*. 2003;25:485–506.
326. Heyland DK, Dodek P, Muscedere J, et al. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med*. 2008;36:737–744.
327. Shorr AF, Zadeikis N, Jackson WL, et al. Levofloxacin for treatment of ventilator-associated pneumonia: a subgroup analysis from a randomized trial. *Clin Infect Dis*. 2005;40: S123–S129.
328. Paladino JA, Sunderlin JL, Forrest A, et al. Characterization of the onset and consequences of pneumonia due to fluoroquinolone-susceptible or -resistant *Pseudomonas aeruginosa*. *J Antimicrob Chemother*. 2003;52:457–463.
329. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. *Clin Infect Dis*. 2016;63:e61–e111.
330. Höffken G, Barth J, Rubinstein E, et al. A randomized study of sequential intravenous/oral moxifloxacin in comparison to sequential intravenous ceftriaxone/oral cefuroxime axetil in patients with hospital-acquired pneumonia. *Infection*. 2007;35:414–420.
331. Stuart Elborn J, Geller DE, Conrad D, et al. A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients. *J Cyst Fibros*. 2015;14:507–514.
331a. Johnson PA, Rodriguez HP, Wazen JJ, et al. Ciprofloxacin versus cefuroxime axetil in the treatment of acute bacterial sinusitis. Sinusitis Infection Study Group. *J Otolaryngol*. 1999;28:3–12.
331b. Adelglass J, DeAbate CA, McElvaine P, et al. Comparison of the effectiveness of levofloxacin and amoxicillin-clavulanate for the treatment of acute sinusitis in adults. *Otolaryngol Head Neck Surg*. 1999;120:320–327.
331c. Adelglass J, Jones TM, Ruoff G, et al. A multicenter, investigator-blinded, randomized comparison of oral levofloxacin and oral clarithromycin in the treatment of acute bacterial sinusitis. *Pharmacother.* 1998;18: 1255–1263.
331d. Burke T, Villanueva C, Mariano H Jr, et al. Comparison of moxifloxacin and cefuroxime axetil in the treatment of acute maxillary sinusitis. Sinusitis Infection Study Group. *Clin Ther*. 1999;21:1664–1677.
331e. Arrieta JR, Galgano AS, Sakano E, et al. Moxifloxacin vs amoxicillin/clavulanate in the treatment of acute sinusitis. *Am J Otolaryngol Head Neck Med Surg*. 2007; 28:78–82.
331f. Poole M, Anon J, Paglia M, et al. A trial of high-dose, short-course levofloxacin for the treatment of acute bacterial sinusitis. *Otolaryngol Head Neck Surg*. 2006;134:10–17.
332. Siegert R, Gehanno P, Nikolaidis P, et al. A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. The sinusitis study group. *Respir Med*. 2000;94:337–344.
333. Hadley JA, Mosges R, Desrosiers M, et al. Moxifloxacin five-day therapy versus placebo in acute bacterial rhinosinusitis. *Laryngoscope*. 2010;120:1057–1062.
334. Grandis JR, Yu VL. Treatment of infections of the ears, nose, and throat and nasal carriage. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:245–250.
335. Levenson MJ, Parisier SC, Dolitsky J, et al. Ciprofloxacin: drug of choice in the treatment of malignant external otitis (MEO). *Laryngoscope*. 1991;101:821–824.
336. Gentry LO. Oral antimicrobial therapy for osteomyelitis. *Ann Intern Med*. 1991;114:986–987.
337. Greenberg RN, Newman MT, Shariaty S, et al. Ciprofloxacin, lomefloxacin, or levofloxacin as treatment for chronic osteomyelitis. *Antimicrob Agents Chemother*. 2000;44:164–166.
338. Bernard L, Waldvogel F, Lew D. Treatment of osteomyelitis and septic arthritis. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:251–258.
339. Peterson LR, Lissack LM, Canter K, et al. Therapy of lower extremity infections with ciprofloxacin in patients with diabetes mellitus, peripheral vascular disease, or both. *Am J Med*. 1989;86:801–808.
340. Lipsky BA, Baker PD, Landon GC, et al. Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. *Clin Infect Dis*. 1997;24:643–648.
341. Raz R, Miron D. Oral ciprofloxacin for treatment of infection following nail puncture wounds of the foot. *Clin Infect Dis*. 1995;21:194–195.
342. Gentry LO, Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. *Antimicrob Agents Chemother*. 1991;35:538–541.
343. Alp E, Koc R, Durak A, et al. Doxycycline plus streptomycin versus ciprofloxacin plus rifampicin in spinal brucellosis. *BMC Infect Dis*. 2006;6:72.
344. Falagas ME, Bliziotis IA. Quinolones for treatment of human brucellosis: critical review of the evidence from microbiological and clinical studies. *Antimicrob Agents Chemother*. 2006;50:22–33.
345. Drancourt M, Stein A, Argenson JN, et al. Oral rifampin plus ofloxacin for treatment of *Staphylococcus*-infected orthopedic implants. *Antimicrob Agents Chemother*. 1993;37:1214–1218.
346. Zimmerli W, Widmer AF, Blatter M, et al. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-body infection (FBI) study group. *JAMA*. 1998;279:1537–1541.
347. Brouqui P, Rousseau MC, Stein A, et al. Treatment of *Pseudomonas aeruginosa*-infected orthopedic prostheses with ceftazidime-ciprofloxacin antibiotic combination. *Antimicrob Agents Chemother*. 1995;39:2423–2425.
348. Barberán J, Aguilar L, Carroquino G, et al. Conservative treatment of staphylococcal prosthetic joint infections in elderly patients. *Am J Med*. 2006;119:993.e7–993.e10.
349. Soriano A, García S, Bori G, et al. Treatment of acute post-surgical infection of joint arthroplasty. *Clin Microbiol Infect*. 2006;12:930–933.
350. Lora-Tamayo J, Euba G, Cobo J, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial. *Int J Antimicrob Agents*. 2016;48:310–316.
351. Barberán J, Aguilar L, Giménez MJ, et al. Levofloxacin plus rifampicin conservative treatment of 25 early staphylococcal infections of osteosynthetic devices for rigid internal fixation. *Int J Antimicrob Agents*. 2008;32:154–157.
352. Gentry LO. Review of quinolones in the treatment of infections of the skin and skin structure. *J Antimicrob Chemother*. 1991;28(supplC):97–110.
353. Karchmer AW. Treatment of skin and soft tissue infections. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:311–321.
354. Powers RD, Schwartz R, Snow RM, et al. Ofloxacin versus cephalexin in the treatment of skin, skin structure, and soft-tissue infections in adults. *Clin Ther*. 1991;13:727–736.
355. Nichols RL, Smith JW, Gentry LO, et al. Multicenter, randomized study comparing levofloxacin and ciprofloxacin for uncomplicated skin and skin structure infections. *South Med J*. 1997;90:1193–1200.
356. Parish LC, Routh HB, Miskin B, et al. Moxifloxacin versus cephalexin in the treatment of uncomplicated skin infections. *Int J Clin Pract*. 2000;54:497–503.
357. Gentry LO, Ramirez-Ronda CH, Rodriguez-Noriega E, et al. Oral ciprofloxacin vs parenteral cefotaxime in the treatment of difficult skin and skin structure infections. A multicenter trial. *Arch Intern Med*. 1989;149:2579–2583.
358. Fass RL, Plouffe JF, Russell JA. Intravenous/oral ciprofloxacin versus ceftazidime in the treatment of serious infections. *Am J Med*. 1989;18(supplD):153–157.
359. Gentry LO, Rodriguez-Gomez G, Zeluff BJ, et al. A comparative evaluation of oral ofloxacin versus intravenous cefotaxime therapy for serious skin and skin structure infections. *Am J Med*. 1989;87:57S–60S.
360. Graham DR, Talan DA, Nichols RL, et al. Once-daily, high-dose levofloxacin versus ticarcillin-clavulanate alone or followed by amoxicillin-clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. *Clin Infect Dis*. 2002;35:381–389.
361. Giordano P, Song J, Pertel P, et al. Sequential intravenous/oral moxifloxacin versus intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate for the treatment of complicated skin and skin structure infection. *Int J Antimicrob Agents*. 2005;26:357–365.
362. Kingsley J, Mehra P, Lawrence LE, et al. A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. *J Antimicrob Chemother*. 2016;71:821–829.
363. Pullman J, Gardovskis J, Farley B, et al. Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a phase 3, double-blind, randomized study. *J Antimicrob Chemother*. 2017;72:3471–3480.
364. Bartlett JG, Inglesby TV, Borio L. Management of anthrax. *Clin Infect Dis*. 2002;35:851–858.
365. Trucksis M, Hooper DC, Wolfson JS. Emerging resistance to fluoroquinolones in staphylococci: an alert. *Ann Intern Med*. 1991;114:424–426.
366. Blumberg HM, Rimland D, Carroll DJ, et al. Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant *Staphylococcus aureus*. *J Infect Dis*. 1991;163:1279–1285.
367. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant *Staphylococcus aureus* clone USA300 in men who have sex with men. *Ann Intern Med*. 2008;148:249–257.
368. Moadebi S, Harder CK, Fitzgerald MJ, et al. Fluoroquinolones for the treatment of pulmonary tuberculosis. *Drugs*. 2007;67:2077–2099.
369. Yew WW, Kwan SY, Ma WK, et al. In-vitro activity of ofloxacin against *Mycobacterium tuberculosis* and its clinical efficacy in multiply resistant pulmonary tuberculosis. *J Antimicrob Chemother*. 1990;26:227–236.
370. Tsukamura M, Nakamura E, Yoshii S, et al. Therapeutic effect of a new antibacterial substance ofloxacin (DL8280) on pulmonary tuberculosis. *Am Rev Respir Dis*. 1985;131:352–356.
371. Mohanty KC, Dhamgaye TM. Controlled trial of ciprofloxacin in short-term chemotherapy for pulmonary tuberculosis. *Chest*. 1993;104:1194–1198.
372. Kennedy N, Berger L, Curram J, et al. Randomized controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. *Clin Infect Dis*. 1996;22:827–833.
373. Johnson JL, Hadad DJ, Boom WH, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2006;10:605–612.
374. Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med*. 2006;174:331–338.
375. Rustomjee R, Lienhardt C, Kanyok T, et al. A phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2008;12:128–138.
376. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371:1577–1587.
377. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med*. 2014;371:1588–1598.
378. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
379. Jacobson KR, Tierney DB, Jeon Cy, et al. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis*. 2010;51:6–14.
380. Devasia RA, Blackman A, Gebretsadik T, et al. Fluoroquinolone resistance in *Mycobacterium tuberculosis:* the effect of duration and timing of fluoroquinolone exposure. *Am J Respir Crit Care Med*. 2009;180:365–370.
381. Chang KC, Leung CC, Yew WW, et al. Newer fluoroquinolones for treating respiratory infection: do they mask tuberculosis? *Eur Respir J*. 2010;35:606–613.
382. Kalita J, Misra UK, Prasad S, et al. Safety and efficacy of levofloxacin versus rifampicin in tuberculous meningitis: an open-label randomized controlled trial. *J Antimicrob Chemother*. 2014;69:2246–2251.
383. Kalita J, Bhoi SK, Betai S, et al. Safety and efficacy of additional levofloxacin in tuberculous meningitis: a randomized controlled pilot study. *Tuberculosis (Edinb)*. 2016;98:1–6.
384. de Lalla F, Maserati R, Scarpellini P, et al. Clarithromycin-ciprofloxacin-amikacin for therapy of *Mycobacterium avium-Mycobacterium intracellulare* bacteremia in patients with AIDS. *Antimicrob Agents Chemother*. 1992;36:1567–1569.
385. Kemper CA, Meng TC, Nussbaum J, et al. Treatment of *Mycobacterium avium* complex bacteremia in AIDS with

a four-drug oral regimen. Rifampin, ethambutol, clofazimine, and ciprofloxacin. The california collaborative treatment group. *Ann Intern Med*. 1992;116:466–472.

386. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med*. 1996;335:377–383.
387. Yew WW, Kwan SY, Ma WK, et al. Ofloxacin therapy of *Mycobacterium fortuitum* infection: further experience. *J Antimicrob Chemother*. 1990;25:880–881.
388. Grosset JH, Ji BH, Guelpa-Lauras CC, et al. Clinical trial of pefloxacin and ofloxacin in the treatment of lepromatous leprosy. *Int J Lepr Other Mycobact Dis*. 1990;58:281–295.
389. Balagon MF, Cellona RV, Abalos RM, et al. The efficacy of a four-week, ofloxacin-containing regimen compared with standard WHO-MDT in PB leprosy. *Lepr Rev*. 2010;81:27–33.
390. Bouza E, Diaz-Lopez MD, Bernaldo de Quiros JC, et al. Ciprofloxacin in patients with bacteremic infections. The Spanish group for the study of ciprofloxacin. *Am J Med*. 1989;87:228S–231S.
391. Regamey C, Steinbach-Lebbin C. Severe infections treated with intravenous ofloxacin: a prospective clinical multicentre Swiss study. *J Antimicrob Chemother*. 1990;26(supplD):107–114.
392. Chan CC, Oppenheim BA, Anderson H, et al. Randomized trial comparing ciprofloxacin plus netilmicin versus piperacillin plus netilmicin for empiric treatment of fever in neutropenic patients. *Antimicrob Agents Chemother*. 1989;33:87–91.
393. Meunier F, Zinner SH, Gaya H, et al. Prospective randomized evaluation of ciprofloxacin versus piperacillin plus amikacin for empiric antibiotic therapy of febrile granulocytopenic cancer patients with lymphomas and solid tumors. The European organization for research on treatment of cancer international antimicrobial therapy cooperative group. *Antimicrob Agents Chemother*. 1991;35:873–878.
394. Giamarellou H, Bassaris HP, Petrikkos G, et al. Monotherapy with intravenous followed by oral high-dose ciprofloxacin versus combination therapy with ceftazidime plus amikacin as initial empiric therapy for granulocytopenic patients with fever. *Antimicrob Agents Chemother*. 2000;44:3264–3271.
395. Peacock JE, Herrington DA, Wade JC, et al. Ciprofloxacin plus piperacillin compared with tobramycin plus piperacillin as empirical therapy in febrile neutropenic patients. A randomized, double-blind trial. *Ann Intern Med*. 2002;137:77–87.
396. Kern WV, Cometta A, de Bock R, et al. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med*. 1999;341:312–318.
397. Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med*. 1999;341:305–311.
398. Rubenstein EB, Rolston K, Benjamin RS, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer*. 1993;71:3640–3646.
399. Kern WV, Marchetti O, Drgona L, et al. Oral antibiotics for fever in low-risk neutropenic patients with cancer: a double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy–EORTC infectious diseases group trial XV. *J Clin Oncol*. 2013;31:1149–1156.
400. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. *Clin Infect Dis*. 2011;52:e56–e93.
401. Winston DJ. Use of quinolone antimicrobial agents in immunocompromised patients. In: Hooper DC, Wolfson JS, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 1993:435–471.
402. Jansen J, Cromer M, Akard L, et al. Infection prevention in severely myelosuppressed patients: a comparison between ciprofloxacin and a regimen of selective antibiotic modulation of the intestinal flora. *Am J Med*. 1994;96:335–341.
403. Laoprasopwattana K, Khwanna T, Suwankeeree P, et al. Ciprofloxacin reduces occurrence of fever in children with acute leukemia who develop neutropenia during chemotherapy. *Pediatr Infect Dis J*. 2013;32:e94–e98.
404. Anonymous. Prevention of bacterial infection in neutropenic patients with hematologic malignancies. A randomized, multicenter trial comparing norfloxacin with ciprofloxacin. The GIMEMA infection program. Gruppo italiano malattie ematologiche maligne dell'adulto. *Ann Intern Med*. 1991;115:7–12.
405. Bow EJ, Mandell LA, Louie TJ, et al. Quinolone-based antibacterial chemoprophylaxis in neutropenic patients: effect of augmented gram-positive activity on infectious morbidity. *Ann Intern Med*. 1996;125:183–190.
406. Broun ER, Wheat JL, Kneebone PH, et al. Randomized trial of the addition of gram-positive prophylaxis to standard antimicrobial prophylaxis for patients undergoing autologous bone marrow transplantation. *Antimicrob Agents Chemother*. 1994;38:576–579.
407. Razonable RR, Litzow MR, Khaliq Y, et al. Bacteremia due to viridans group streptococci with diminished susceptibility to levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. *Clin Infect Dis*. 2002;34:1469–1474.
408. Timmers GJ, Dijstelbloem Y, Simoons-Smit AM, et al. Pharmacokinetics and effects on bowel and throat microflora of oral levofloxacin as antibacterial prophylaxis in neutropenic patients with haematological malignancies. *Bone Marrow Transplant*. 2004;33:847–853.
409. Timmers GJ, Simoons-Smit AM, Leidekker ME, et al. Levofloxacin vs. ciprofloxacin plus phenethicillin for the prevention of bacterial infections in patients with haematological malignancies. *Clin Microbiol Infect*. 2007;13:497–503.
410. Cruciani M, Malena M, Bosco O, et al. Reappraisal with meta-analysis of the addition of gram-positive prophylaxis to fluoroquinolone in neutropenic patients. *J Clin Oncol*. 2003;21:4127–4137.
411. Cattaneo C, Quaresmini G, Casari S, et al. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant *Escherichia coli* among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. *J Antimicrob Chemother*. 2008;61:721–728.
412. Reuter S, Kern WV, Sigge A, et al. Impact of fluoroquinolone prophylaxis on reduced infection-related mortality among patients with neutropenia and hematologic malignancies. *Clin Infect Dis*. 2005;40:1087–1093.
413. Kern WV. Epidemiology of fluoroquinolone-resistant *Escherichia coli* among neutropenic patients. *Clin Infect Dis*. 1998;27:235–237.
414. Hafez HA, Yousif D, Abbassi M, et al. Prophylactic levofloxacin in pediatric neutropenic patients during autologous hematopoietic stem cell transplantation. *Clin Transplant*. 2015;29:1112–1118.
415. Le TP, Yeaman MR, Bayer AS. Treatment of experimental and human bacterial endocarditis with quinolone antimicrobial agents. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:259–273.
416. Dworkin RJ, Lee BL, Sande MA, et al. Treatment of right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers with ciprofloxacin and rifampin. *Lancet*. 1989;2:1071–1072.
417. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *Am J Med*. 1996;101:68–76.
418. Yebra M, Ortigosa J, Albarran F, et al. Ciprofloxacin in a case of Q fever endocarditis. *N Engl J Med*. 1990;323:614.
419. Raoult D, Houpikian P, Dupont HT, et al. Treatment of Q fever endocarditis-comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. *Arch Intern Med*. 1999;159:167–173.
420. Tunkel AR, Scheld WM. Treatment of bacterial meningitis and other central nervous system infections. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:275–289.
421. Scotton PG, Pea F, Giobbia M, et al. Cerebrospinal fluid penetration of levofloxacin in patients with spontaneous acute bacterial meningitis. *Clin Infect Dis*. 2001;33:E109–E111.
422. Pea F, Pavan F, Nascimben E, et al. Levofloxacin disposition in cerebrospinal fluid in patients with external ventriculostomy. *Antimicrob Agents Chemother*. 2003;47:3104–3108.
423. Segev S, Rosen N, Joseph G, et al. Pefloxacin efficacy in gram-negative bacillary meningitis. *J Antimicrob Chemother*. 1990;26:187–192.
424. Schonwald S, Beus I, Lisic M, et al. Ciprofloxacin in the treatment of gram-negative bacillary meningitis. *Am J Med*. 1989;87:248S–249S.
425. Krcméry V Jr, Filka J, Uher J, et al. Ciprofloxacin in treatment of nosocomial meningitis in neonates and in infants: report of 12 cases and review. *Diagn Microbiol Infect Dis*. 1999;35:75–80.
426. Wong-Beringer A, Beringer P, Lovett MA. Successful treatment of multidrug-resistant *Pseudomonas aeruginosa* meningitis with high-dose ciprofloxacin. *Clin Infect Dis*. 1997;25:936–937.
427. Dworzack DL, Sanders CC, Horowitz EA, et al. Evaluation of single-dose ciprofloxacin in the eradication of *Neisseria meningitidis* from nasopharyngeal carriers. *Antimicrob Agents Chemother*. 1988;32:1740–1741.
428. Gilja OH, Halstensen A, Digranes A, et al. Use of single-dose ofloxacin to eradicate tonsillopharyngeal carriage of *Neisseria meningitidis*. *Antimicrob Agents Chemother*. 1993;37:2024–2026.
429. Cuevas LE, Kazembe P, Mughogho GK, et al. Eradication of nasopharyngeal carriage of *Neisseria meningitidis* in children and adults in rural Africa: a comparison of ciprofloxacin and rifampicin. *J Infect Dis*. 1995;171:728–731.
430. Wu HM, Harcourt BH, Hatcher CP, et al. Emergence of ciprofloxacin-resistant *Neisseria meningitidis* in north America. *N Engl J Med*. 2009;360:886–892.
431. Limaye AP, Hooper CJ. Treatment of tularemia with fluoroquinolones: two cases and review. *Clin Infect Dis*. 1999;29:922–924.
432. Chocarro A, Gonzalez A, Garcia I. Treatment of tularemia with ciprofloxacin. *Clin Infect Dis*. 2000;31:623.
433. Holley HP Jr. Successful treatment of cat-scratch disease with ciprofloxacin. *JAMA*. 1991;265:1563–1565.
434. Raoult D, Drancourt M. Antimicrobial therapy of rickettsial diseases. *Antimicrob Agents Chemother*. 1991;35:2457–2462.
435. Rolain JM, Raoult D. Treatment of intracellular infections. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:323–335.
436. Lang R, Rubinstein E. Quinolones for the treatment of brucellosis. *J Antimicrob Chemother*. 1992;29:357–360.
437. Akova M, Uzun O, Akalin HE, et al. Quinolones in treatment of human brucellosis: comparative trial of ofloxacin-rifampin versus doxycycline-rifampin. *Antimicrob Agents Chemother*. 1993;37:1831–1834.
438. McClean KL, Hitchman D, Shafran SD. Norfloxacin is inferior to chloroquine for falciparum malaria in northwestern Zambia: a comparative clinical trial. *J Infect Dis*. 1992;165:904–907.
439. Watt G, Shanks GD, Edstein MD, et al. Ciprofloxacin treatment of drug-resistant falciparum malaria. *J Infect Dis*. 1991;164:602–604.
440. Leung AY, Chan MT, Yuen KY, et al. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis*. 2005;40:528–537.
441. Knoll GA, Humar A, Fergusson D, et al. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. *JAMA*. 2014;312:2106–2114.
442. Kale-Pradhan PR, Zhao JJ, Palmer JR, et al. The role of antimicrobials in Crohn's disease. *Expert Rev Gastroenterol Hepatol*. 2013;7:281–288.
443. Kim ES, Hooper DC. Clinical importance and epidemiology of quinolone resistance. *Infect Chemother*. 2014;46:226–238.
444. Blaser J, Stone BB, Groner MC, et al. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. *Antimicrob Agents Chemother*. 1987;31:1054–1060.
445. Drlica K, Zhao X. Mutant selection window hypothesis updated. *Clin Infect Dis*. 2007;44:681–688.
446. Drusano GL, Liu W, Brown DL, et al. Impact of short-course quinolone therapy on susceptible and resistant populations of *Staphylococcus aureus*. *J Infect Dis*. 2009;199:219–226.
447. Low DE. Quinolone resistance and its clinical relevance. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:355–386.
448. Parry MF, Panzer KB, Yukna ME. Quinolone resistance. Susceptibility data from a 300-bed community hospital. *Am J Med*. 1989;87:12S–16S.
449. Kresken M, Wiedemann B. Development of resistance to nalidixic acid and the fluoroquinolones after the introduction of norfloxacin and ofloxacin. *Antimicrob Agents Chemother*. 1988;32:1285–1288.
450. Coronado VG, Edwards JR, Culver DH, et al. Ciprofloxacin resistance among nosocomial *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the United States. *Infect Control Hosp Epidemiol*. 1995;16:71–75.
451. Schmitz FJ, Jones ME, Hofmann B, et al. Characterization of *grlA, grlB, gyrA,* and *gyrB* mutations in 116 unrelated isolates of *Staphylococcus aureus* and effects of mutations on ciprofloxacin MIC. *Antimicrob Agents Chemother*. 1998;42:1249–1252.
452. Tillotson GS, Draghi DC, Sahm DF, et al. Susceptibility of *Staphylococcus aureus* isolated from skin and wound infections in the United States 2005-07: laboratory-based

surveillance study. *J Antimicrob Chemother*. 2008;62:109–115.

453. Holmes RL, Jorgensen JH. Inhibitory activities of 11 antimicrobial agents and bactericidal activities of vancomycin and daptomycin against invasive methicillin-resistant *Staphylococcus aureus* isolates obtained from 1999 through 2006. *Antimicrob Agents Chemother*. 2008;52:757–760.
454. Otter JA, French GL. The emergence of community-associated methicillin-resistant *Staphylococcus aureus* at a London teaching hospital, 2000-2006. *Clin Microbiol Infect*. 2008;14:670–676.
455. Turner PJ. Trends in antimicrobial susceptibilities among bacterial pathogens isolated from patients hospitalized in European medical centers: 6-year report of the MYSTIC surveillance study (1997-2002). *Diagn Microbiol Infect Dis*. 2005;51:281–289.
456. Pegues DA, Colby C, Hibberd PL, et al. The epidemiology of resistance to ofloxacin and oxacillin among clinical coagulase-negative staphylococcal isolates: analysis of risk factors and strain types. *Clin Infect Dis*. 1998;26:72–79.
457. Hooper DC. Fluoroquinolone resistance among gram-positive cocci. *Lancet Infect Dis*. 2002;2:530–538.
458. Tanaka M, Matsumoto T, Kobayashi I, et al. Emergence of in vitro resistance to fluoroquinolones in *Neisseria gonorrhoeae* isolated in Japan. *Antimicrob Agents Chemother*. 1995;39:2367–2370.
459. Wang SA, Harvey AB, Conner SM, et al. Antimicrobial resistance for *Neisseria gonorrhoeae* in the United States, 1988 to 2003: the spread of fluoroquinolone resistance. *Ann Intern Med*. 2007;147:81–88.
460. Ison CA, Woodford PJ, Madders H, et al. Drift in susceptibility of *Neisseria gonorrhoeae* to ciprofloxacin and emergence of therapeutic failure. *Antimicrob Agents Chemother*. 1998;42:2919–2922.
461. Ng PPL, Chan RK, Ling AE. Gonorrhoea treatment failure and ciprofloxacin resistance. *Int J STD AIDS*. 1998;9:323–325.
462. Aplasca de los Reyes MR, Pato-Mesola V, Klausner JD, et al. A randomized trial of ciprofloxacin versus cefixime for treatment of gonorrhea after rapid emergence of gonococcal ciprofloxacin resistance in the Philippines. *Clin Infect Dis*. 2001;32:1313–1318.
463. Endtz HP, Ruijs GJ, van Klingeren B, et al. Quinolone resistance in *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *J Antimicrob Chemother*. 1991;27:199–208.
464. Endtz HP, Mouton RP, van der Reyden T, et al. Fluoroquinolone resistance in *Campylobacter* spp. isolated from human stools and poultry products. *Lancet*. 1990;335:787.
465. Lautenbach E, Strom BL, Nachamkin I, et al. Longitudinal trends in fluoroquinolone resistance among enterobacteriaceae isolates from inpatients and outpatients, 1989-2000: differences in the emergence and epidemiology of resistance across organisms. *Clin Infect Dis*. 2004;38:655–662.
466. Zervos MJ, Hershberger E, Nicolau DP, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991-2000. *Clin Infect Dis*. 2003;37:1643–1648.
467. Karlowsky JA, Kelly LJ, Thornsberry C, et al. Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States. *Antimicrob Agents Chemother*. 2002;46:2540–2545.
468. Karlowsky JA, Jones ME, Thornsberry C, et al. Trends in antimicrobial susceptibilities among enterobacteriaceae isolated from hospitalized patients in the United States from 1998 to 2001. *Antimicrob Agents Chemother*. 2003;47:1672–1680.
469. Ena J, Amador C, Martinez C, et al. Risk factors for acquisition of urinary tract infections caused by ciprofloxacin resistant *Escherichia coli*. *J Urol*. 1995;153:117–120.
470. Oethinger M, Conrad S, Kaifel K, et al. Molecular epidemiology of fluoroquinolone-resistant *Escherichia coli* bloodstream isolates from patients admitted to European cancer centers. *Antimicrob Agents Chemother*. 1996;40:387–392.
471. Carratala J, Fernandez-Sevilla A, Tubau F, et al. Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis*. 1995;20:557–560.
472. Cometta A, Marchetti O, Calandra T, et al. In vitro antimicrobial activity of moxifloxacin against bacterial strains isolated from blood of neutropenic cancer patients. *Eur J Clin Microbiol Infect Dis*. 2006;25:537–540.
473. Pena C, Albareda JM, Pallares R, et al. Relationship between quinolone use and emergence of ciprofloxacin-resistant *Escherichia coli* in bloodstream infections. *Antimicrob Agents Chemother*. 1995;39:520–524.
474. Carratala J, Fernandez-Sevilla A, Tubau F, et al. Emergence of fluoroquinolone-resistant *Escherichia coli* in fecal flora of cancer patients receiving norfloxacin prophylaxis. *Antimicrob Agents Chemother*. 1996;40:503–505.
475. Garau J, Xercavins M, Rodríguez-Carballeira M, et al. Emergence and dissemination of quinolone-resistant *Escherichia coli* in the community. *Antimicrob Agents Chemother*. 1999;43:2736–2741.
476. Blanco JE, Blanco M, Mora A, et al. Prevalence of bacterial resistance to quinolones and other antimicrobials among avian *Escherichia coli* strains isolated from septicemic and healthy chickens in Spain. *J Clin Microbiol*. 1997;35:2184–2185.
477. Hooper DC. New uses for new and old quinolones and the challenge of resistance. *Clin Infect Dis*. 2000;30:243–254.
478. Johnson JR, Tchesnokova V, Johnston B, et al. Abrupt emergence of a single dominant multidrug-resistant strain of *Escherichia coli*. *J Infect Dis*. 2013;15:919–928.
479. Lautenbach E, Metlay JP, Bilker WB, et al. Association between fluoroquinolone resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections: the role of inadequate empirical antimicrobial therapy. *Clin Infect Dis*. 2005;41:923–929.
480. Camins BC, Marschall J, DeVader SR, et al. The clinical impact of fluoroquinolone resistance in patients with *E. coli* bacteremia. *J Hosp Med*. 2011;6:344–349.
481. Adam HJ, Schurek KN, Nichol KA, et al. Molecular characterization of increasing fluoroquinolone resistance in *Streptococcus pneumoniae* isolates in Canada, 1997 to 2005. *Antimicrob Agents Chemother*. 2007;51:198–207.
482. Ho PL, Yung RWH, Tsang DNC, et al. Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: results of a Hong Kong multicentre study in 2000. *J Antimicrob Chemother*. 2001;48:659–665.
483. Fenoll A, Aguilar L, Granizo JJ, et al. Has the licensing of respiratory quinolones for adults and the 7-valent pneumococcal conjugate vaccine (PCV-7) for children had herd effects with respect to antimicrobial non-susceptibility in invasive *Streptococcus pneumoniae*? *J Antimicrob Chemother*. 2008;62:1430–1433.
484. Karlowsky JA, Thornsberry C, Jones ME, et al. Factors associated with relative rates of antimicrobial resistance among *Streptococcus pneumoniae* in the United States: results from the TRUST surveillance program (1998-2002). *Clin Infect Dis*. 2003;36:963–970.
485. Nichol KA, Adam HJ, Karlowsky JA, et al. Increasing genetic relatedness of ciprofloxacin-resistant *Streptococcus pneumoniae* isolated in Canada from 1997 to 2005. *Antimicrob Agents Chemother*. 2008;52:1190–1194.
486. Richter SS, Heilmann KP, Beekmann SE, et al. The molecular epidemiology of *Streptococcus pneumoniae* with quinolone resistance mutations. *Clin Infect Dis*. 2005;40:225–235.
487. Sahm DF, Peterson DE, Critchley IA, et al. Analysis of ciprofloxacin activity against *Streptococcus pneumoniae* after 10 years of use in the United States. *Antimicrob Agents Chemother*. 2000;44:2521–2524.
488. Davies TA, Yee YC, Goldschmidt R, et al. Decline in the prevalence of pandemic clones Spain23F-1 and Spain9V-3 among US fluoroquinolone-resistant *Streptococcus pneumoniae* TRUST surveillance isolates since 2001. *Postgrad Med*. 2008;120:39–45.
489. Jacobs MR, Good CE, Bajaksouzian S, et al. Emergence of *Streptococcus pneumoniae* serotypes 19a, 6c, and 22f and serogroup 15 in cleveland, Ohio, in relation to introduction of the protein-conjugated pneumococcal vaccine. *Clin Infect Dis*. 2008;47:1388–1395.
490. Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med*. 2006;354:1455–1463.
491. LaPlante KL, Rybak MJ, Tsuji B, et al. Fluoroquinolone resistance in *Streptococcus pneumoniae*: area under the concentration-time curve/MIC ratio and resistance development with gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin. *Antimicrob Agents Chemother*. 2007;51:1315–1320.
492. Florea NR, Tessier PR, Zhang C, et al. Pharmacodynamics of moxifloxacin and levofloxacin at simulated epithelial lining fluid drug concentrations against *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2004;48:1215–1221.
493. Davies TA, Evangelista A, Pfleger S, et al. Prevalence of single mutations in topoisomerase type II genes among levofloxacin-susceptible clinical strains of *Streptococcus pneumoniae* isolated in the United States in 1992 to 1996 and 1999 to 2000. *Antimicrob Agents Chemother*. 2002;46:119–124.
494. Richardson DC, Bast D, McGeer A, et al. Evaluation of susceptibility testing to detect fluoroquinolone resistance mechanisms in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2001;45:1911–1914.
495. Mandell LA, Peterson LR, Wise R, et al. The battle against emerging antibiotic resistance: should fluoroquinolones be used to treat children? *Clin Infect Dis*. 2002;35:721–727.
496. Jumbe NL, Louie A, Miller MH, et al. Quinolone efflux pumps play a central role in emergence of fluoroquinolone resistance in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2006;50:310–317.
497. Jumbe N, Louie A, Leary R, et al. Application of a mathematical model to prevent in vivo amplification of antibiotic-resistant bacterial populations during therapy. *J Clin Invest*. 2003;112:275–285.
498. Lode H, Rubinstein E. Adverse effects. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:407–419.
499. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Saf*. 2009;32:359–378.
500. Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis*. 2005;41: S144–S157.
501. Stevens V, Dumyati G, Fine LS, et al. Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. *Clin Infect Dis*. 2011;53:42–48.
502. Norrby SR. Central nervous system toxicity. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:461–465.
503. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. *Drug Saf*. 2011;34: 465–488.
504. Halliwell RF, Davey PG, Lambert JJ. Antagonism of GABAA receptors by 4-quinolones. *J Antimicrob Chemother*. 1993;31:457–462.
505. Jones SC, Sorbello A, Boucher RM. Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review. *Drug Saf*. 2011;34:839–847.
506. Etminan M, Brophy JM, Samii A. Oral fluoroquinolone use and risk of peripheral neuropathy: a pharmacoepidemiologic study. *Neurology*. 2014;83:1261–1263.
507. Sodhi M, Sheldon CA, Carleton B, et al. Oral fluoroquinolones and risk of secondary pseudotumor cerebri syndrome: nested case-control study. *Neurology*. 2017;89:792–795.
508. Ball P, Mandell L, Patou G, et al. A new respiratory fluoroquinolone, oral gemifloxacin: a safety profile in context. *Int J Antimicrob Agents*. 2004;23:421–429.
509. Iannini P, Mandell L, Patou G, et al. Cutaneous adverse events and gemifloxacin: observations from the clinical trial program. *J Chemother*. 2006;18:3–11.
510. Blanca-López N, Andreu I, Torres Jaén MJ. Hypersensitivity reactions to quinolones. *Curr Opin Allergy Clin Immunol*. 2011;11:285–291.
511. Ferguson J. Fluoroquinolone photosensitization: a review of clinical and laboratory studies. *Photochem Photobiol*. 1995;62:954–958.
512. Ferguson J. Phototoxicity due to fluoroquinolones. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:451–460.
513. Stahlmann R. Effects on connective tissue structures. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:441–449.
514. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. *Clin Infect Dis*. 1997;25:1196–1204.
515. Adam D. Use of quinolones in pediatric patients. *Rev Infect Dis*. 1989;11:S1113–S1116.
516. Schaad UB, Wedgwood J. Lack of quinolone-induced arthropathy in children. *J Antimicrob Chemother*. 1992;30:414–416.
517. Schaad UB, abdus Salam M, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an international society of chemotherapy commission. *Pediatr Infect Dis J*. 1995;14:1–9.
518. Zabraniecki L, Negrier I, Vergne P, et al. Fluoroquinolone induced tendinopathy: report of 6 cases. *J Rheumatol*. 1996;23:516–520.
519. Van der Linden PD, Sturkenboom MCJM, Herings RMC, et al. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med*. 2003;163: 1801–1807.

520. Barge-Caballero E, Crespo-Leiro MG, Paniagua-Martín MJ, et al. Quinolone-related achilles tendinopathy in heart transplant patients: incidence and risk factors. *J Heart Lung Transplant*. 2008;27:46–51.
521. Van der Linden PD, Sturkenboom MCJM, Herings RMC, et al. Fluoroquinolones and risk of achilles tendon disorders: case-control study. *BMJ*. 2002;324:1306–1307.
522. Wise BL, Peloquin C, Choi H, et al. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med*. 2012;125:1228 e1223–1228 e1228.
523. Sendzik J, Shakibaei M, Schäfer-Korting M, et al. Fluoroquinolones cause changes in extracellular matrix, signalling proteins, metalloproteinases and caspase-3 in cultured human tendon cells. *Toxicology*. 2005;212:24–36.
524. Etminan M, Forooghian F, Brophy JM, et al. Oral fluoroquinolones and the risk of retinal detachment. *JAMA*. 2012;307:1414–1419.
525. Kuo SC, Chen YT, Lee YT, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis*. 2014;58:197–203.
526. Pasternak B, Svanström H, Melbye M, et al. Association between oral fluoroquinolone use and retinal detachment. *JAMA*. 2013;310:2184–2190.
527. Lee CC, Lee MT, Chen YS, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med*. 2015;175:1839–1847.
528. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015;5:e010077.
529. Yap YG, Camm AJ. QT prolongation with quinolone antimicrobial agents. In: Hooper DC, Rubinstein E, eds. *Quinolone Antimicrobial Agents*. Washington, DC: American Society for Microbiology Press; 2003:421–440.
530. Chou H-W, Wang J-L, Chang C-H, et al. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and β-lactam/β-lactamase inhibitors: a Taiwanese nationwide study. *Clin Infect Dis*. 2015;60:566–577.
531. Inghammar M, Svanström H, Melbye M, et al. Oral fluoroquinolone use and serious arrhythmia: bi-national cohort study. *BMJ*. 2016;352:i843.
532. Noel GJ, Natarajan J, Chien S, et al. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther*. 2003;73:292–303.
533. Morganroth J, Dimarco JP, Anzueto A, et al. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. *Chest*. 2005;128:3398–3406.
534. Briasoulis A, Agarwal V, Pierce WJ. QT prolongation and torsade de pointes induced by fluoroquinolones: infrequent side effects from commonly used medications. *Cardiology*. 2011;120:103–110.
535. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. *Int J Antimicrob Agents*. 2007;29:374–379.
536. Ball P, Mandell L, Niki Y, et al. Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Saf*. 1999;21:407–421.
537. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: review of 95 cases. *Clin Infect Dis*. 1994;18:946–950.
538. Paterson JM, Mamdani MM, Manno M, et al. Fluoroquinolone therapy and idiosyncratic acute liver injury: a population-based study. *CMAJ*. 2012;184:1565–1570.
539. Anonymous. Hypoglycemia and hyperglycemia with fluoroquinolones. *Med Lett Drugs Ther*. 2003;45:64.
540. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med*. 2006;354:1352–1361.
541. Lewis RJ, Mohr JF. Dysglycaemias and fluoroquinolones. *Drug Saf*. 2008;31:283–292.
542. Pugi A, Longo L, Bartoloni A, et al. Cardiovascular and metabolic safety profiles of the fluoroquinolones. *Expert Opin Drug Saf*. 2012;11:53–69.
543. Berkovitch M, Pastuszak A, Gazarian M, et al. Safety of the new quinolones in pregnancy. *Obstet Gynecol*. 1994;84:535–538.
544. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. 1998;42:1336–1339.
545. Bar-Oz B, Moretti ME, Boskovic R, et al. The safety of quinolones—meta-analysis of pregnancy outcomes. *Eur J Obstet Gynecol Reprod Biol*. 2009;143:75–78.
546. Bebear CM, de Barbeyrac B, Pereyre S, et al. Activity of moxifloxacin against the urogenital mycoplasmas *Ureaplasma* spp., *Mycoplasma hominis* and *Mycoplasma genitalium* and *Chlamydia trachomatis*. *Clin Microbiol Infect*. 2008;14:801–805.
547. Pfaller MA, Sader HS, Rhomberg PR, et al. In vitro activity of delafloxacin against contemporary bacterial pathogens from the United States and Europe, 2014. *Antimicrob Agents Chemother*. 2017;61.
548. Harnett SJ, Fraise AP, Andrews JM, et al. Comparative study of the in vitro activity of a new fluoroquinolone, ABT-492. *J Antimicrob Chemother*. 2004;53:783–792.
549. Soge OO, Salipante SJ, No D, et al. In vitro activity of delafloxacin against clinical *Neisseria gonorrhoeae* isolates and selection of gonococcal delafloxacin resistance. *Antimicrob Agents Chemother*. 2016;60:3106–3111.
550. Hammerschlag MR, Roblin PM. The in vitro activity of a new fluoroquinolone, ABT-492, against recent clinical isolates of *Chlamydia pneumoniae*. *J Antimicrob Chemother*. 2004;54:281–282.
551. Waites KB, Crabb DM, Duffy LB. Comparative in vitro susceptibilities and bactericidal activities of investigational fluoroquinolone ABT-492 and other antimicrobial agents against human mycoplasmas and ureaplasmas. *Antimicrob Agents Chemother*. 2003;47:3973–3975.
552. Almer LS, Hoffrage JB, Keller EL, et al. In vitro and bactericidal activities of ABT-492, a novel fluoroquinolone, against Gram-positive and Gram-negative organisms. *Antimicrob Agents Chemother*. 2004;48:2771–2777.
553. Cercenado E, Marin M, Sanchez-Martinez M, et al. In vitro activities of tigecycline and eight other antimicrobials against different *Nocardia* species identified by molecular methods. *Antimicrob Agents Chemother*. 2007;51:1102–1104.
554. Lai CC, Tan CK, Lin SH, et al. Comparative in vitro activities of nemonoxacin, doripenem, tigecycline and 16 other antimicrobials against *Nocardia brasiliensis, Nocardia asteroides* and unusual *Nocardia* species. *J Antimicrob Chemother*. 2009;64:73–78.
555. Flamm RK, Rhomberg PR, Huband MD, et al. In vitro activity of delafloxacin tested against isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. *Antimicrob Agents Chemother*. 2016;60:6381–6385.
556. Sano C, Tatano Y, Shimizu T, et al. Comparative in vitro and in vivo antimicrobial activities of sitafloxacin, gatifloxacin and moxifloxacin against *Mycobacterium avium*. *Int J Antimicrob Agents*. 2011;37:296–301.
557. Kohno Y, Ohno H, Miyazaki Y, et al. In vitro and in vivo activities of novel fluoroquinolones alone and in combination with clarithromycin against clinically isolated *Mycobacterium avium* complex strains in Japan. *Antimicrob Agents Chemother*. 2007;51:4071–4076.
558. Disratthakit A, Doi N. In vitro activities of DC-159a, a novel fluoroquinolone, against *Mycobacterium* species. *Antimicrob Agents Chemother*. 2010;54:2684–2686.
559. Tomioka H, Sato K, Kajitani H, et al. Comparative antimicrobial activities of the newly synthesized quinolone WQ-3034, levofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. *Antimicrob Agents Chemother*. 2000;44:283–286.

36 Unique Antibacterial Agents

Gerard R. Barber

SHORT VIEW SUMMARY

- The US Food and Drug Administration (FDA) has granted each of several novel antibacterials a Qualified Infectious Disease Product (QIDP) designation. Whether their activity is chiefly directed against gram-negative or gram-positive pathogens, or both, each of these agents has been developed to combat multidrug-resistant organisms/pathogens (MDROs).

Plazomicin (Zemdri)

- A new aminoglycoside (AG)
- Binds to bacterial 30S ribosomal subunit, inhibiting protein synthesis
- Indicated for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis
- Seemed to produce good outcomes and clearance of carbapenem-resistant Enterobacteriaceae (CRE) from bloodstream infections; larger trial numbers are needed
- Predominantly a gram-negative–active agent to MDROs, including CRE. As with other AGs, seems to exhibit synergy when paired with various other β-lactam agents
- Requires therapeutic drug monitoring, serum trough levels <3 μg/mL to avoid nephrotoxicity in treating cUTI
- More involved pharmacokinetics/pharmacodynamics (PK/PD) may be needed to determine optimal dosing for deeper infection
- Boxed warnings for nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm

Cefiderocol

- Most advanced among "Trojan horse" antibacterials
- Siderophore (iron-binding) antipseudomonal catechol cephalosporin
- Solely gram-negative activity
- Broad spectrum over gram-negative MDROs across Ambler classes A to D of β-lactamases, demonstrates enhanced stability compared with cefepime, ceftazidime, and meropenem
- Question remains regarding which infectious indications will be pursued
- PK/PD modeling suggests doses of 2 g and 3 g via extended 2.5-hour infusions at every-8-hour intervals for optimization in subjects with normal renal function
- Dose reduction needed for diminished renal function

Meropenem-Vaborbactam (Vabomere)

- Combination antipseudomonal carbapenem/cyclic boronic acid β-lactamase inhibitor
- Broad gram-negative (including MDROs), gram-positive, and solid anaerobe coverage
- Labeled indication: (community-acquired) cUTI, including pyelonephritis
- Off-label use likely to include complicated intraabdominal infections (cIAIs), hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP)
- Niche will be extended-spectrum β-lactamase (ESBL)/CRE infections, especially in penicillin-allergic patients
- Dose: 4 g intravenous piggyback (IVPB) every 8 hours via 3-hour infusion, requires dose and/or interval reduction with reduced renal function

Fosfomycin (Contepo)

- First epoxide antibacterial
- Oral form already approved in United States for single-dose lower tract UTI, IV form long approved outside United States
- Expected New Drug Application (NDA) initially for cUTI, potential for numerous other indications, given characteristics mentioned later
- Potent MDRO activity against gram-negative and gram-positive organisms and has demonstrated activity to ceftazidime-avibactam–resistant *Klebsiella pneumoniae* carbapenemases (KPCs)
- A late April 2019 FDA Complete Response Letter cited concerns for facility inspections, and manufacturing deficiencies could possibly delay potential drug approval date.
- Varied anaerobe activity
- Cross-sensitivity to other antibacterials not reported
- Good distribution into lung, bone, and cerebrospinal fluid
- Evidence of additive or synergistic properties when combined with other antimicrobial classes, such as β-lactams, carbapenems, lipoglycopeptides, AGs, polypeptides, and glycylcyclines
- For severe resistant infections, recommended to be given with other antibacterials and not as monotherapy
- 330 mg sodium per 1 g fosfomycin, so attention needed for electrolyte abnormalities, especially in fragile populations; can perhaps be useful in conjunction with amphotericin B in patients having fungal coinfection

Omadacycline (Nuzyra)

- An aminomethylcycline derived from tetracycline
- Active against pathogens possessing tetracycline resistance mechanisms
- IV and oral formulations advantageous for step-down therapy; one study showed extravasation rates 1.5-fold higher than comparator
- Epithelial lining fluid (ELF) and alveolar macrophage concentrations surpass serum concentrations
- Demonstrated activity against gram-negative, gram-positive, and atypical respiratory pathogens. Activity against other MDROs and selected sexually transmitted disease pathogens. No activity against *Pseudomonas* spp.
- One study demonstrating acceptable outcomes with conventional dosing in high body mass index subjects and diabetic subjects
- Does not require dose adjustment for renal dysfunction, including hemodialysis
- Should have a niche for stewardship and placement among penicillin-allergic or patients with intolerance to other antibacterial classes

Eravacycline (Xerava)

- Fully synthetic fluorocycline with resemblance to tetracycline reference structure
- Active against pathogens possessing tetracycline resistance mechanisms
- IV formulation only
- Indication: cIAI. Anticipate other off-label use on hospital floors, intensive care units, and outpatient infusion centers
- Broad gram-positive and gram-negative coverage, including MDROs. Very good activity against *Bacteroides fragilis* but variable non-*fragilis Bacteroides* activity
- Good atypical respiratory pathogen coverage and achievement of pulmonary concentrations but pneumonia indications not pursued
- Not active against *Pseudomonas* spp.
- Opportunities to spare carbapenems and quinolones for stewardship and intolerant patients, a potent agent with activity against ESBL-, KPC-, New Delhi metallo-β-lactamase (NDM)-, and oxacillinase (OXA)-producing *Klebsiella* spp.
- 1 mg/kg IVPB every-12-hour dosing, renal adjustment not necessary

Lefamulin

- First systemic pleuromutilin
- IV and oral formulations
- NDA for community-acquired bacterial pneumonia anticipated in fourth quarter of 2018

SHORT VIEW SUMMARY—cont'd

- Broad activity—gram-positive and gram-negative community respiratory pathogens, including *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*, as well as atypical bacteria: *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*
- Small study of healthy subjects suggests 5.7-fold higher ELF concentrations compared with serum, as well as good adipose and skeletal tissue penetration
- Acute bacterial skin and skin structure infection (ABSSSI) studies entering phase III
- Possesses potent in vitro activity against common gram-positive skin organisms, including *Staphylococcus aureus* (methicillin-sensitive *S. aureus* [MSSA] and methicillin-resistant *S. aureus* [MRSA]), coagulase-negative *Staphylococcus* spp., *Streptococcus agalactiae*, and *Streptococcus pyogenes*
- Good MRSA activity and skeletal penetration suggest a potential off-label role for prolonged step-down therapy (IV dosing is every 12 hours)
- Seemingly well tolerated
- Niche for stewardship and reducing selective pressures of quinolones, use in intolerant patients with opportunity for oral step-down therapies

Iclaprim

- Inhibits bacterial dihydrofolate reductase
- Bears some structural similarity to trimethoprim
- A gram-positive active agent demonstrating good activity against β-hemolytic streptococci, *Staphylococcus aureus* (MSSA and MRSA)
- QIDP status ABSSSI and HABP
- NDA for ABSSSI submitted; in February 2019 received an FDA Complete Response Letter citing concerns for hepatotoxicity and the need for additional patient data
- Iclaprim does have FDA orphan drug status for the treatment of *S. aureus* pulmonary infections in patients with cystic fibrosis
- IV formulation only
- Would not require renal dose adjustment
- Older studies using weight-based dosing seemed to show an association of cardiac toxicity associated with higher serum concentrations; for ABSSSI, acceptable serum concentrations obtained used a fixed dosing regimen of 80 mg/kg IV every 12 hours

Antimicrobial resistance long preceded the advent of the penicillin era. This "modern antibiotic age" of antibacterials brought enormous and immediate improvements to global public health. Still, the declaration that infectious diseases were forever cured was short lived, as briefly after the introduction of penicillin was the arrival of penicillin-resistant *Staphylococcus aureus* noted in the hospital environment. Today's rapid and welcome technologic advances have created faster and economical modes of travel, capable computers, and electronic data transfer. Regarding medicine, these advances serve to enable increasingly aggressive medical therapies and diagnostic tools. However, an Infectious Diseases Society of America (IDSA) report in 2009 showed that within the pharmaceutical industry, only three new antibacterial compounds were in advanced stages of clinical development.[1] Until about 2010 drug manufacture for the previous 3 decades shifted away from the creation of "unique antibacterial" agents having novel mechanisms to favor medication development for chronic diseases, oncology, and niche diagnoses. Thus the current challenges of the emergence and distribution of multidrug-resistant organisms (MDROs) pose a significant burden not only to health care institutions but the community as well.

The Generating Antibiotic Incentives Now (GAIN) provisions and US Food and Drug Administration (FDA) stance (Table 36.1) augmented the activism of organizations such as IDSA against the drought in the antibiotic pipeline. In 2010 the IDSA's 10 × '20 Initiative[2] was a call to develop 10 new safe and effective antibacterials by the year 2020. A good deal of the most pressing, current MDROs include methicillin-resistant *S. aureus* (MRSA); penicillin-resistant *Streptococcus pneumoniae*; vancomycin-resistant enterococci; fluoroquinolone-, extended spectrum cephalosporin-, and recently, carbapenem-resistant *Klebsiella pneumoniae*; *Escherichia coli*; and *Pseudomonas* spp. All of these and other clinically relevant gram-negative bacteria[3] are listed among the GAIN provisions' "qualifying pathogens" posing significant threat to public health (see Table 36.1).

Thus there is an urgent need to develop antibacterials that preferably are bactericidal in action and have a high therapeutic index, a targeted spectrum of antimicrobial activity that limits perturbation of the normal host microbiota, and a low potential for promoting drug resistance.[4] In this chapter are summaries of "novel antibacterials," most in later stages of development, with potential for future clinical utility.

A summary in the order in which this chapter's novel antibacterials are listed can be seen in Table 36.2.

TABLE 36.1 The GAIN Provisions

In July 2012 Generating Antibiotic Incentives Now (GAIN) was signed into US law. GAIN provisions are part of the US Food and Drug Administration (FDA) Safety and Innovation Act. The intent of GAIN was to make antibacterial and antifungal antibiotics a more valuable commodity of drug class to pharmaceutical manufacturers.

Brief points about GAIN provisions:

- Allows, by law, a designation of Qualified Infectious Disease Product (QIDP) status to antibacterial or antifungal drugs developed for humans with the intention of treating serious or life-threatening infections;
- QIDP status granted to a new antimicrobial status effects a 5-year market protection or exclusivity to the manufacturer that distances competition from generic manufacturers. This QIDP 5-year protection would be in addition to any other market exclusivities already granted by law;
- QIDP-designated antimicrobials receive FDA fast-track and priority review status and are also granted an expedited FDA-approval process;
- The FDA will compile and at minimum, every 5 years update a list of "qualifying" pathogens that pose significant risk to public health (see link later);
- The FDA will review and update antibiotic guidance from a regulatory and scientific perspective and issue newly developed guidance on pathogen-focused antibiotics;
- The FDA will draft preliminary guidance for manufacturers seeking to develop antibiotics addressing unmet needs, including agents that are narrowly targeted or pathogen focused.

Dalbavancin (Dalvance) was the first antibacterial agent to receive QIDP status and ceftolozane-tazobactam (Zerbaxa) the first antibacterial with gram-negative activity to receive the designation. Every agent in this current chapter and each antibacterial discussed in the full text of Chapter 35, 8th edition, *Principles and Practice of Infectious Disease*, has been granted QIDP status (with the exception of LFF571, which has been deleted from Novartis development).

Federal Register. Establishing a List of Qualifying Pathogens Under the Food and Drug Administration Safety and Innovation Act. https://www.federalregister.gov/documents/2014/06/05/2014-13023/establishing-a-list-of-qualifying-pathogens-under-the-food-and-drug-administration-safety-and. Accessed February 27, 2018.

MULTIDRUG-RESISTANT BACTERIA

Plazomicin (ACHN-490)

Plazomicin (Zemdri; Achaogen, San Francisco) is a next-generation AG derived from the AG sisomicin, which was the parent compound from which 400 derivatives were evaluated.[5] A New Drug Application (NDA) had been filed for plazomicin for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis and bloodstream infections (BSIs) due to certain Enterobacteriaceae in patients who have limited or no alternative treatment options. However, this "neoglycoside" with Qualified Infectious Disease Product (QIDP) status instead received FDA approval in late June 2018 only for the treatment of cUTIs, including pyelonephritis caused by certain Enterobacteriaceae in patients who have limited or no alternative treatment options.

The increasing frequency of gram-negative MDROs has renewed interest in the utility of the AG class, long ignored with the arrival of agents such as tigecycline, linezolid (LZD), niche β-lactams, and carbapenems, and also because AG-induced nephrotoxicity and ototoxicity are potentially serious concerns. Development of drug resistance to tobramycin and amikacin among clinical gram-negative isolates has been less often observed when compared with advanced-generation cephalosporins, monobactams, and carbapenems. This combined with improved knowledge of pharmacokinetics/pharmacodynamics (PK/PD) of AGs based on monitoring of serum levels has led to markedly improved ototoxicity profiles and their use in combination with β-lactam agents.[6,7]

TABLE 36.2 Summary of Activities of Novel Antibacterial Agents

DRUG NAME	DRUG CLASS	TARGET	ACTIVITY AGAINST RESISTANT GRAM-NEGATIVE PATHOGENS	ACTIVITY AGAINST RESISTANT GRAM-POSITIVE PATHOGENS	INDICATIONS (1 = FDA-LABELED INDICATION) (2 = ANTICIPATED NDA FILING) (3 = ANTICIPATED OFF-LABEL USE)
Plazomicin (Zemdri)	Aminoglycoside	30S ribosomal subunit	Yes	No	**1.** cUTI (adults), including pyelonephritis, caused by certain Enterobacteriaceae in patients who have limited or no alternative treatment options **2, 3.** Deeper-seated infections, such as bloodstream infections, HABPs, VABPs, and cIAIs caused by certain Enterobacteriaceae in patients who have limited or no alternative treatment options
Cefiderocol	Siderophore Cephalosporin	PBP	Yes	No	**2, 3.** Health care–associated and hospital-acquired bacterial pneumonias, VABPs, and carbapenem-resistant organisms at various sites
Meropenem-vaborbactam (Vabomere)	β-Lactam (carbapenem) + β-lactamase inhibitor	PBP; β-lactamase	Yes	No	**1.** cUTIs, including pyelonephritis in adults **2, 3.** cIAIs, HABPs and VABPs with suspicion of MDROs
Fosfomycin (Contepo)	Phosphonic acid derivative	Phosphoenolpyruvate synthetase	Yes	Yes	**2, 3.** cUTI, including pyelonephritis; cIAIs, HABPs, and VABPs; added to existing therapies for demonstrated MDRO infections
Omadacycline	Aminomethylcycline	30S ribosomal subunit	Yes	Yes	**2.** CABP, ABSSSIs, possibly uncomplicated UTIs and cUTIs if trials are pursued
Eravacycline (Xerava)	Fluorocycline	30S ribosomal subunit	Yes	Yes	**1.** cIAIs
Lefamulin	Pleuromutilin	50S ribosomal subunit	No	Yes	**1.** ABSSSIs **2.** CABP
Iclaprim	Diaminopyrimidine	Dihydrofolate reductase	No	Yes	**2.** ABSSSIs **2, 3.** Various bacterial pneumonias (CABP, HABP, VABP)

ABSSSIs, Acute bacterial skin and skin structure infections; *CABP,* community-acquired bacterial pneumonia; *cIAIs,* complicated intraabdominal infections; *cUTI,* complicated urinary tract infection; *HABP,* hospital-acquired bacterial pneumonia; *MDRO,* multidrug-resistant organism; *NDA,* New Drug Application; *PBP,* penicillin-binding protein; *VABP,* ventilator-associated bacterial pneumonia.
Modified from The Pew Charitable Trusts at http://www.pewtrusts.org/-/media/assets/2018/03/antibiotics_clinical_dev_table_february2018.pdf.

A second phase I study, among eight subjects, age 18 to 65 years (the earlier phase I study was among 39 adults), examined the highest dose from the first study of this concentration-dependent agent at 15 mg/kg given once daily for a shorter duration of 5 days, attempting to mimic the same cumulative exposures from the earlier study. In these healthy subjects it appears that the area under the concentration-time curve (AUC) and maximum serum concentration (C_{max}) of plazomicin increase linearly and proportionately in accordance with increasing doses, without accumulation when given in a once-daily regimen; conversely, elimination of the drug is independent of plazomicin dose. Similar to gentamicin, tobramycin, and particularly amikacin, the plasma protein binding of ACHN-490 is relatively low at 16% (±5), with plasma AUC values high relative to potential pathogens. The investigators extrapolate that in *E. coli* having minimal inhibitory concentrations (MICs) of ≤1 μg/mL and *K. pneumoniae* with MICs of ≤0.5 μg/mL, AUC/MIC target attainment of 80 and 160, respectively, should be achievable at a once-daily dose of 7 mg/kg.[8] Renal safety was assessed with estimated creatinine clearance using the Cockcroft-Gault formula. Ototoxicity was measured by pure tone audiometry with bone conduction and otoacoustic emission at baseline, the end of treatment, and at 3 and 6 months posttreatment. Electronystagmography tested vestibular function at the same time intervals. ACHN-490 was well tolerated. Headache, tinnitus, dizziness, and somnolence of mild-to-moderate severity were the most commonly encountered adverse events (AEs), all being transient and rapidly resolving. Tinnitus had occurred in two patients at higher dose ranges, with both subjects retaining normal cochlear and vestibular function.

A phase II multinational study compared plazomicin (10 mg/kg or 15 mg/kg) to IV levofloxacin, 750 mg each once daily for 5 days, in the treatment of cUTI and pyelonephritis. Randomized at a 2:1 ratio, plazomicin to levofloxacin, a total of 145 subjects were enrolled (22, 76, and 47 subjects to plazomicin 10 mg/kg, plazomicin 15 mg/kg, and levofloxacin 750 mg, respectively); median age was 39 and 43 years, respectively, with *E. coli* ($n = 69$) the most common pathogen among Enterobacteriaceae ($n = 84$). Serious adverse events occurred in 1 patient receiving plazomicin deemed unrelated, and 2 levofloxacin study patients (1 related, 1 unrelated). Unilateral, permanent tinnitus was reported for 1 plazomicin patient dosed at 15 mg/kg. Mild increases in serum creatinine (SCr) deemed transient, but clinically relevant, occurred in 5 plazomicin subjects and 1 receiving levofloxacin. However, 1 patient receiving plazomicin did not have resolution of their rising SCr at late follow-up (LFU). In the modified intent-to-treat population, microbiologic eradication rates (MBE) at test-of-cure (TOC) for plazomicin 15 mg/kg and levofloxacin were each approximately 59%, whereas the rate of MBE for plazomicin 10 mg/kg was 50%. Microbiologic eradication rates in the microbiologically evaluable population at TOC were 85.7%, 88.6%, and 81% for plazomicin 10 mg/kg, plazomicin 15 mg/kg, and levofloxacin 750 mg, respectively. Investigators concluded that rates of MBE at TOC were similar across all arms, although rates of microbiologic recurrence were higher among subjects receiving levofloxacin.[9]

Plazomicin demonstrated greater activity against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates having aminoglycoside-modifying enzymes (AGME) than isolates with altered permeability/efflux. From 16 New York City–area hospitals, 407 *A. baumannii* and 679 *P. aeruginosa* isolates from 2009 were analyzed, comparing ACHN-490 to gentamicin, tobramycin, and amikacin. Against *A. baumannii* isolates, the MIC_{90} of ACHN-490 was 16 μg/mL compared with >64 μg/mL for gentamicin, tobramycin, and amikacin, respectively. Against *P. aeruginosa* isolates, the ACHN-490 MIC was 32 μg/mL, compared with >64, 64, and 16 μg/mL of gentamicin, tobramycin, and amikacin, respectively.[10] Breakpoints for Zemdri are not yet established.

A synergy study reviewed the activity of ACHN-490 alone and when combined with either cefepime, doripenem, imipenem-cilastatin, or piperacillin-tazobactam against 25 clinical isolates from the United States and Poland of *P. aeruginosa* from blood, urine, wounds, and the respiratory tract. Four strains exhibited resistant AGME phenotypes, with 3 having *ant*(2")-Ia and another *acc*(6')-Ib.[11] Investigators found identical MICs to plazomicin for susceptible or resistant phenotypes. Synergy was defined as a ≥2-$\log_{10}$ decrease in colony-forming units (CFUs)/mL 24 hours after exposure to the drug combination versus active drug alone. At 24 hours individual MIC ranges were plazomicin, 0.5 to 256 μg/mL; cefepime, 1 to 256 μg/mL; doripenem, 0.12 to 256 μg/mL; imipenem-cilastatin, 0.25 to 512 μg/mL; and piperacillin-tazobactam, 2 to 4096 μg/mL. At 24 hours plazomicin with each of the four agents demonstrated synergy against most strains, imipenem-cilastatin/plazomicin showing the least synergy at 68% of isolates, whereas the piperacillin-tazobactam/plazomicin combination was greatest at 92%. Antagonism was not seen among any of the four combinations. It seems clinical validation assessing the efficacy of plazomicin plus piperacillin-tazobactam is warranted for *P. aeruginosa* and other MDROs.

Among 493 clinical blood and nasal isolates of MRSA collected from 23 US hospitals in 2009 and 2010, plazomicin demonstrated greater activity than either tobramycin or amikacin but similar activity to gentamicin.[12] Unlike gram-negative bacteria, only three AGME are produced by *S. aureus* isolates that may influence variable activity of the AGs.

In addition, the Biomedical Advanced Research and Development Authority has granted funds to the manufacturer of ACHN-490 to investigate plazomicin as potential treatment for *Yersinia pestis* and *Francisella tularensis* biowarfare.[13]

The phase III CARE (Combating Antibiotic Resistant Enterobacteriaceae) trial was an open-label, multicenter, pathogen-specific study comparing plazomicin with colistin in patients with serious carbapenem-resistant Enterobacteriaceae (CRE) infection. A total of 69 patients were divided into two cohorts. In cohort 1 ($n = 39$), 29 of 30 patients with a BSI were confirmed to have CRE infection. Subjects were randomized to plazomicin, 15 mg/kg intravenous piggyback (IVPB) daily, or colistin, 300 mg IVPB load, followed by 5 mg/kg/day, each arm also receiving either high-dose, extended-infusion meropenem or tigecycline for BSI or hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) infections. Plazomicin, colistin, and meropenem were dose adjusted according to renal function. Cohort 2 enrolled 30 subjects having BSI, HABP/VABP, or cUTI with or without acute pyelonephritis (AP). In this observational arm there were 15 BSI, with 14 confirmed due to CRE. These subjects were generally less acute than those in cohort 1, but several did have concomitant infection with *P. aeruginosa* or *Acinetobacter* spp., which qualified as exclusion criteria in the randomized cohort. Both cohorts received 7 to 14 days IVPB study drug for BSI and HABP/VABP, whereas for cUTI/AP patients in cohort 2, the protocol-specified treatment was 4 to 7 days of IVPB plazomicin, followed by optional oral therapy for 7 to 14 days of total therapy. Follow-up included a 7-day test of cure (TOC; from the last dose of IVPB study drug), 14-day end of study, and 60-day LFU.

Clearance of CRE bacteremia by study day 5 was observed in 12 of 14 (85.7%) plazomicin-based subjects compared with 7 of 15 (46.7%) subjects receiving colistin-based therapy. Persistence of CRE bacteremia more than 5 days after initiation of the study drug was found to be a significant disease-related complication associated with higher rates of 28-day all-cause mortality and also death at 60 days, both of which were higher in the colistin arm. Safety profiles also favored plazomicin with regard to serious adverse events related to the study drug among the randomized cohort, 1 of 14 (7.1%) to 4 of 16 (25%), plazomicin to colistin, respectively; no serious adverse events related to plazomicin were observed in observational cohort 2. Specifically, regarding renal function, postbaseline rise of ≥0.5 mg/dL SCr and overall magnitude of increase of SCr were greater among the colistin-treated subjects. Among plazomicin-treated subjects there was a higher incidence ($n = 6$) of SCr elevations >0.5 mg/dL; 4 subjects were <1 mg/dL and 2 were <1.5 mg/dL. Instances of ototoxicity or death related to the study drug were not noted in either cohort.[14]

In a multinational, double-blinded study termed "EPIC" (European Prospective Investigation into Cancer and Nutrition), among 609 randomized subjects, plazomicin (15 mg/kg IVPB daily) was compared with meropenem (1 g IVPB every 8 hours) for the treatment of cUTI or AP for 7 to 10 days duration. After 4 days of IVPB therapy, transition to oral levofloxacin in either arm was permitted. All drugs were dose adjusted per renal function. A primary efficacy end point was a composite of microbiologic eradication (baseline uropathogen $\geq 10^6$ CFUs/mL reduced to $<10^4$ CFUs/mL) in microbiologically modified intent-to-treat subjects and clinical cure at study day 5 and TOC (approximately day 17 after study initiation). Nearly 64% of the study population ($n = 388$) had a uropathogen susceptible to plazomicin and meropenem. Day 5 composite cure rates were similar: 88% to 91.4%, plazomicin to meropenem, respectively, whereas the composite cure at TOC demonstrated statistical superiority for plazomicin, 81.7% (156/191) to 70.1% (138/197) meropenem. A LFU visit at approximately day 28 also favored plazomicin over meropenem, 77% to 60.4%, respectively. Ototoxicity was observed in 1 subject in each arm, both with complete resolution. Rates of SCr increases ±0.5 mg/dL during IV therapy were similar (3.7% and 3%) among plazomicin and meropenem subjects, respectively, but among plazomicin subjects it was reported that in 2 of 11 subjects SCr had not returned to baseline by the LFU visit.

Also from the EPIC study, regarding MDRO and DROs, in a subgroup of microbiologically modified intent-to-treat patients with an extended spectrum β-lactamase (ESBL)-positive phenotype (MIC >2 μg/mL for aztreonam, ceftazidime, or ceftriaxone), microbiologic eradication was achieved in 42 of 51 (82.4%) and 45 of 60 (75.0%) for plazomicin and meropenem, respectively. Another subgroup of microbiologically modified intent-to-treat patients with AG-nonsusceptible pathogens (nonsusceptibility to amikacin, gentamicin, or tobramycin per 2016 Clinical and Laboratory Standards Institute [CLSI] criteria), microbiologic eradication was achieved in 41 of 52 (78.8%) and 35 of 51 (68.6%) for plazomicin and meropenem, respectively.[15,16]

At the LFU visit (day 28 ± 4 days), 147 of 191 (77.0%) of the plazomicin-treated patients and 119 of 197 (60.4%) meropenem-treated patients achieved composite cure. Clinical cure was similar between the plazomicin and meropenem treatment groups, 169 of 191 (88.5%) and 168 of 197 (85.3%), respectively. Microbiologic eradication was achieved in 161 of 191 (84.3%) and 128 of 197 (65.0%) of plazomicin and meropenem patients, respectively.

In conclusion, Zemdri is a recently approved AG with potent activity against MDR gram-negative pathogens, including CRE. As with other AGs, it is expected that plazomicin will demonstrate synergistic activity when combined with certain other antibacterials. A good understanding of resistance mechanisms most prevalent among an institution's pathogens should be helpful in directing empirical therapy of plazomicin for cUTI and other critical off-label uses. Despite good outcomes and some important lessons learned regarding time to clearance of CRE from blood in the small CARE trial, the FDA issued a complete response letter and denied the drug's approval for deeper-seated MDRO infections. Still, a niche for plazomicin utilization to combat CRE will be as a colistin-sparing agent. For cUTIs Zemdri will require dose adjustment in patients with diminished renal function, and the labeled dosing schema differs somewhat from the other concentration-dependent killing AGs and includes recommendations for therapeutic drug monitoring of serum plazomicin trough levels <3 μg/mL in patients having an estimated creatinine clearance of 15 to 89 mL/min. Zemdri labeling also includes black box warnings for nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm.

Cefiderocol (S-649266)

Cefiderocol (Shionogi & Co, Osaka, Japan) is in the most advanced stages of trials among the siderophore, or iron-binding, antibacterials. It is an antipseudomonal catechol-cephalosporin with a novel, "Trojan horse," mechanism. Cefiderocol binds to ferric iron and is actively transported into bacterial cells through the outer cell membrane via bacterial iron transporters whose chief function is to deliver necessary iron nutrients to the bacterial cells (Fig. 36.1).

A small study of S-649266's stability to clinical isolates with β-lactamases, including metallo-β-lactamases (MBLs) and class A and D carbapenemases, showed impressive results, including withstanding hydrolysis by *Klebsiella pneumoniae* carbapenemases (KPCs), MP-1,

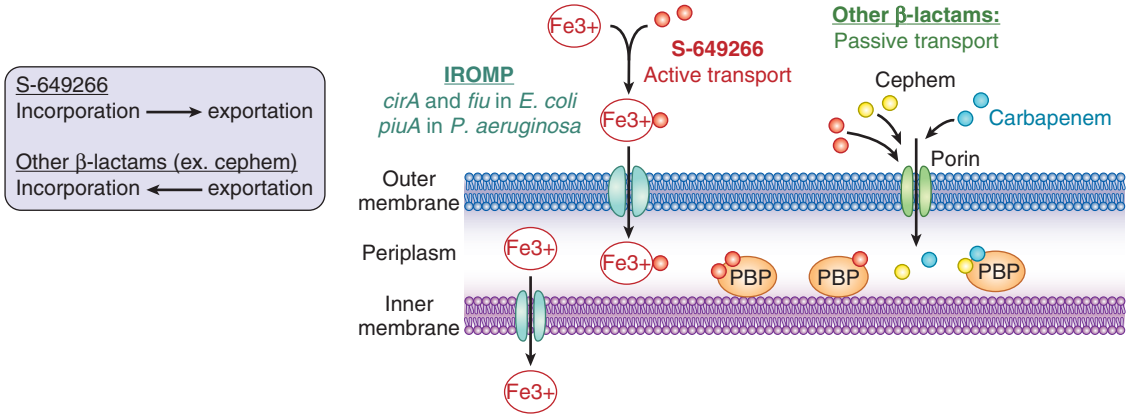

FIG. 36.1 Cefiderocol (S-649266); among Trojan horse antibacterials: a novel way to circumvent gram-negative bacterial resistance. *IROMP,* Iron-regulated outer membrane protein; *PBP,* penicillin-binding protein. *(From Tillotson G. Trojan horse antibiotics: a novel way to circumvent gram-negative bacterial resistance?* Infect Dis (Auckl). *2016;9:45–52.)*

Verona integron-coded metallo-β-lactamase 2 (VIM)-2, L1, and New Delhi metallo-β-lactamase 1 (NDM-1) when compared with cefepime, ceftazidime, and meropenem.[17]

In vitro studies of S-649266 activity against clinical isolates of nonfermenting gram-negative bacteria and Enterobacteriaceae seem to demonstrate the drug's potent activity. Compared with cefepime, meropenem, piperacillin-tazobactam, and levofloxacin against global isolates of *A. baumannii* ($n = 104$), *P. aeruginosa* ($n = 104$), and *Stenotrophomonas maltophila* ($n = 108$), S-649266 exhibited a demonstrably lower range of MICs and MIC_{90} for all isolates than its comparators. For *P. aeruginosa*, β-lactamase–producing strains ($n = 33$) were predominantly VIM and IMP. Composite $MIC_{50/90}$ for S-649266 was 0.5 and 4 μg/mL, respectively, compared with $MIC_{50/90}$ of >64 μg/mL (cefepime), >32 μg/mL (meropenem), and 128 μg/mL and >256 μg/mL (piperacillin-tazobactam).[18] Using a cation-adjusted Mueller-Hinton broth for the siderophore versus CLSI breakpoints for comparators, S-649266 activity was assessed among 850 global isolates of *E. coli, K. pneumoniae, Serratia marcescens, Citrobacter freundii, Enterobacter aerogenes,* and *Enterobacter cloacae*. In a first set of 617 isolates, containing 233 β-lactamase producers, MICs were ≤1 μg/mL, except for 8 isolates having an MIC of ≥8 μg/mL. A second set, including 116 KPC and class B metallo-carbapenemase producers, showed MICs of ≤4 μg/mL for all except 7 isolates, which showed MICs of ≥16 μg/mL. These high-MIC isolates left investigators uncertain but believing reduced porin influx due to deficient iron transport may be responsible.[19] Among 1221 global isolates, including 679 varied oxacillinase (OXA)-producers of meropenem, nonsusceptible Enterobacteriaceae, *P. aeruginosa,* and *A. baumannii* demonstrated cefiderocol having generally lower MICs compared with ceftazidime, ceftolozane-tazobactam, and colistin.[20]

The completed (late 2016) APEKs-cUTI phase III trial was an international multicenter double-blinded comparison of subjects randomized 2:1 cefiderocol, 2 g IVPB every 8 hours, versus imipenem-cilastatin, 1 g IVPB every 8 hours. Both antibacterials were infused over a 1-hour period in a trial of 448 subjects with cUTIs with or without pyelonephritis due to gram-negative bacteria. A median duration of therapy was 9 hospital days among each arm; switch to oral therapy was not permitted. A TOC visit approximately 7 days after the completion of therapy showed cefiderocol treatment noninferior to imipenem-cilastatin meeting composite end points of clinical cure and microbiologic eradication. Among the 371 modified intent-to-treat subjects, these rates were 72.6% (183/252) for cefiderocol to 54.6% (65/119) for imipenem-cilastatin. The FDA composite end points and per patient microbiologic response at TOC both demonstrated statistical superiority as well. Investigators reported a lower number of cefiderocol-related adverse reactions than for its comparator.[21]

One-gram to 2-g doses of cefiderocol exhibit linear PK characteristics. As 60% to 70% of the drug is eliminated by the kidneys, renal dose adjustments will be needed for patients having diminished renal function, as well as supplemental dosing for hemodialysis patients. With a terminal half-life of approximately 2.5 hours, every-8-hours dosing appears appropriate for normal function. Monte Carlo modeling suggests that a 3-hour infusion will optimize bactericidal effect and that perhaps every-6-hours dosing should be considered in subjects having augmented renal function.[22]

As of early 2018, other phase III trials of cefiderocol were ongoing. One, named APEK-NP, is a multicenter double-blind comparison to meropenem, each with adjunctive LZD, for health care–associated bacterial pneumonia, HABP, and VABP, anticipating enrollment of 300 subjects with completion in early 2019 (ACT 03032380).[23] Another, CREDIBLE-CR, is an open-label multicenter investigation of SH-689266 to "best available therapy" (BAT) for the treatment of carbapenem-resistant organisms causing infection at various sites, including pneumonias, cUTI, sepsis, and BSIs, expecting about 150 subjects (ACT 02714595).[24]

In all, the novel mechanism enhancing the penetrability of this siderophore-cephalosporin, as well as demonstrable stability to β-lactamases, presents a gram-negative antibacterial with potent and very broad activity. Should it receive FDA or European Medicines Agency (EMA) approval based on efficacy and safety results, it would be a welcome addition as treatment against drug-resistant gram-negative pathogens, including *Stenotrophomonas* spp.

In conclusion, cefiderocol is an iron-binding, antipseudomonal, catechol-cephalosporin with broad activity against gram-negative aerobic bacteria. It is largely devoid of activity against gram-positive and anaerobic organisms that do not display an affinity for ferric iron uptake. Similar to ceftazidime, cefiderocol displays a decided affinity for penicillin-binding protein 3 among nonfermenting gram-negatives, such as *P. aeruginosa* and *A. baumannii* as well as *Enterobacteriaceae*. However, cefiderocol's potent gram-negative activity thus far demonstrates the ability to withstand resistance mechanisms among CRE, KPC, and MBL-producing organisms. The drug seems to be well tolerated; whether or not the variability of human subject physiology of ferric iron stores and uptake mechanisms will influence outcomes of clinical cure in infection caused by questionably susceptible pathogens remains a subject of debate. Further question remains regarding the submission of which infectious indications are to be pursued by the manufacturer.

Meropenem-Vaborbactam (Vabomere)

Vaborbactam (Melinta Therapeutics, New Haven, CT), formerly known as RPX7009 and developed by Rempex Pharmaceuticals, is classed as a cyclic boronic acid β-lactamase inhibitor (BLI), which is a subclass of serine BLIs. Boronic acids have been studied as inhibitors of serine proteases, such as the serine carbapenemases that can be produced by strains of KPC. Vaborbactam is the second non–β-lactam BLI receiving FDA approval after NXL104 (avibactam) in combination with ceftazidime. Earlier, as RPX7009, it had been tested in combination with biapenem, a carbapenem approved in Japan and studied in complicated intra-abdominal infections (cIAIs).[25–27]

In the United States vaborbactam was mated to the antipseudomonal carbapenem, meropenem, and studied in two phase III clinical trials coined TANGO 1 and TANGO 2.[28] TANGO was the acronym for *T*argeting *A*ntibiotic *N*onsusceptible *G*ram-Negative *O*rganisms. According to the GAIN provisions, meropenem-vaborbactam is an example of a pathogen-focused antibacterial.

TANGO 1 was a multicenter, randomized, double-blind, double-dummy study of adult subjects with cUTI, including AP. There were 550 randomly assigned (1:1) subjects receiving either meropenem-vaborbactam (4 g [as meropenem 2 g plus vaborbactam 2 g] IVPB as 3-hour infusion) or piperacillin-tazobactam (4.5 g IVPB as 30-minutes infusion) each 8 hours for up to 10 days. Subjects meeting defined protocol criteria for improvement could be switched to oral levofloxacin after 5 days of parenteral therapy. Patients were well matched regarding demographics, cUTI strata (AP, cUTI with or without removable source of infection), and among microbiologically modified intent-to-treat subjects ($n = 374$), gram-negative pathogen. The mean duration of IV therapy among both arms was 8 days. With FDA-defined end points, meropenem-vaborbactam was deemed noninferior to piperacillin-tazobactam, actually achieving superiority for clinical cure or improvement and microbiologic eradication ($<10^4$ CFUs/mL) at end of IV therapy visit, 98.4% (183/186 subjects) to 94.3% (165/175 subjects), respectively. Among 12 microbiologically modified intent-to-treat subjects treated with meropenem-vaborbactam having concurrent bacteremia at baseline, clinical and microbiologic response was successful in 10 subjects (83%). For meropenem-vaborbactam, higher rates of transaminitis, headache, and phlebitis were observed, although rates of discontinuation due to study drug AEs were lower than that of piperacillin-tazobactam, 2.9% versus 5.1%, respectively.

TANGO 2 was an open-label, multicenter study across 27 sites in nine countries of meropenem-vaborbactam compared with BAT, randomized 2:1. Chosen clinical sites were known to have a high incidence of KPC-producing CRE, and eligible adult subjects had a confirmed diagnosis of serious infection, such as bacteremia and/or HABP/VABP, cIAI, or cUTI, and expected to receive IV antimicrobial therapy ≥7 to 14 days. Duration of therapy could be extended beyond 14 days, and mean duration was approximately 29 days. Enrollment also allowed patients with impaired renal function, including subjects on hemodialysis.[29]

Meropenem-vaborbactam 4 g (as meropenem 2 g plus vaborbactam 2 g) was given IVPB over 3 hours every 8 hours; BAT was defined as IV antibacterials either alone or in combination: carbapenems (imipenem, meropenem, ertapenem), AGs (gentamicin, tobramycin, amikacin), polypeptides (colistin, polymyxin B), tigecycline, or monotherapy with ceftazidime-avibactam.

Primary efficacy end points differed by infection but included the proportion of patients with a clinical outcome of cure at end of therapy (EOT) and TOC based on assessment of signs and symptoms across all infection types. Also included was all-cause mortality at day 28 across all infection types. The modified carbapenem-resistant Enterobacteriaceae (mCRE) modified intent-to-treat subpopulation ($n = 43$) were subjects meeting the microbiologically modified intent-to-treat criteria and having confirmed meropenem-resistant Enterobacteriaceae at baseline. *K. pneumoniae* accounted for 86% of baseline pathogens. These mCRE–modified intent-to-treat subjects, with 28 in the meropenem-vaborbactam arm and 15 in BAT, were considered as a primary efficacy population.

By all indications, clinical cure at EOT (64.3%–33.3%) and TOC (57.1%–26.7%) favored meropenem-vaborbactam over BAT, respectively, both with statistical significance. Microbiologic cure, evaluated across all infection types of confirmed CRE infection at EOT and TOC visits, also favored meropenem-vaborbactam (63.3% and 50%, respectively) compared with BAT (40% and 33.3%, respectively). Also, across all infection types, all-cause 28-day mortality was higher among the BAT arm compared with meropenem-vaborbactam, as were sepsis-related deaths, numbering 4 to 1, respectively. Renal-related AEs and proportions of subjects with increases in SCr of ≥0.5 mg/dL also favored meropenem-vaborbactam.

In another subset of patients from TANGO 2, 19 subjects deemed immunocompromised (4 leukemia/lymphoma, 5 medication, 10 transplant), 18 of whom were confirmed CRE, clinical cure rates at EOT and TOC, as well as 28-day all-cause mortality, favored meropenem-vaborbactam therapy over BAT.[30]

In conclusion, in August 2017 the FDA granted approval of meropenem-vaborbactam for cUTIs, including pyelonephritis. FDA-recognized antimicrobial susceptibility test interpretive criteria (STIC) for Enterobacteriaceae are (1) Susceptible ≤4/8 μg/mL; (2) Intermediate 8/8 μg/mL; and (3) Resistant ≥16/8 μg/mL. As with meropenem alone, meropenem-vaborbactam will require renal dose adjustment. With favorable disposition for patients having severe penicillin allergy and its broad spectrum of activity, including gram-negative MDROs and solid antianaerobic coverage, meropenem-vaborbactam as monotherapy or combined with other antibacterials will likely be used for numerous off-label indications in intensive care unit (ICU) settings and among other seriously ill patients.

Fosfomycin (ZTI-01, Contepo): Intravenous

Fosfomycin (Nabriva Therapeutics, Dublin, Ireland [formerly Zolyd, Zavante Therapeutics, San Diego, CA]) is the first of the epoxide class of antimicrobials. Originally named phosphonomycin, it is a broad-spectrum bactericidal agent active against resistant gram-negative and gram-positive microorganisms. Through inhibition of phosphoenol-pyruvate synthetase, fosfomycin blocks formation of *N*-acetylmuramic acid, ultimately interfering with early cell wall synthesis.[31,32] Discovered in Spain in the late 1960s, IV and oral formulations have been in clinical use for decades outside the United States, with the oral form approved in the United States since 1996 for uncomplicated UTIs. With phase III trials (ZEUS) completed for cUTI,[33] including AP, ZTI-01 has also received FDA QIDP status for numerous, current late-phase I trials, including cIAI, HABP, VABP, and acute bacterial skin and skin-structure infections (ABSSSI).

The ZEUS phase III trials were multinational, randomized, double-blinded studies among 465 hospitalized subjects with cUTI or AP. Comparing 6 g of ZTI-01 to 4.5 g of piperacillin-tazobactam, each administered every 8 hours as 1-hour infusions, the antibiotics were given for a 7-day duration, although up to 14 days of therapy was permissible in patients with a concurrent bacteremia. Transition to oral therapy was not allowed. ZTI-01 met its noninferiority objective compared with piperacillin-tazobactam, having similar rates of overall success (64.7% vs. 54.5%, respectively), clinical cure at TOC (day 19, 90.8% vs. 91.6%, respectively), and treatment-emergent adverse events (TEAEs). Most TEAEs to ZTI-01 were reported to be mild and with transient gastrointestinal (GI) effects not necessitating discontinuation of study drug. No deaths occurred in the study, and serious AEs were reportedly uncommon (five, ZTI-01 vs. six, piperacillin-tazobactam). Within ZEUS, among the microbiologically modified intent-to-treat cases, 34% of subjects exhibited isolates from urine or blood by MIC indicative of phenotypic resistance for ESBL (31%, ≥2 μg/mL aztreonam, ceftazidime, or ceftriaxone), CRE (6.1%, ≥4 μg/mL imipenem or meropenem), Amino-R (17%, gentamicin or amikacin), or MDR (19%, nonsusceptibility ≥3 classes of antimicrobials). The numbers of resistant isolates to each arm were balanced and clinical cure rates high, but eradication rates were notably higher in the ZTI-01 arm.[34]

The SENTRY surveillance program in 2015 collected a total of 2200 gram-negative and gram-positive isolates from US medical centers. Using established FDA breakpoints for oral fosfomycin tromethamine, the program examined the drug's activity against a total 96% of those isolates, finding high activity against Enterobacteriaceae; 100% of randomly selected *E. coli* were sensitive to fosfomycin—$MIC_{50/90,}$ 0.5/1 μg/mL, whereas *K. pneumoniae* exhibited an $MIC_{50/90}$ of 4/16 μg/mL, 97% of isolates of these isolates having a ≤64 μg/mL. Fosfomycin exhibited less activity against *P. aeruginosa*—$MIC_{50/90}$ of 64/128 μg/mL and *A. baumannii-calcoaceticus* complex, $MIC_{50/90}$ of 128/256 μg/mL. The drug did well against *Enterococcus faecalis* isolates, exhibiting 99% sensitivity, 1% as intermediate, whereas MICs were higher among *Enterococcus faecium* isolates. Among a very small number (<30) of gram-negative anaerobes, fosfomycin MICs to *Bacteroides fragilis* group were variable, whereas activity was described as limited against *Prevotella* spp. As in several in vitro studies using established FDA or CLSI breakpoints of the fosfomycin oral formulation with its limited bioavailability, a further

conclusion was that the IV formulation will necessitate a reevaluation of breakpoints.[35]

Owing to its unique structure and class, to date fosfomycin has not been shown to incur cross-resistance to other antimicrobial classes. This and favorable characteristics for achieving meaningful serum and tissue distribution, including lung, cerebrospinal fluid, and bone, have led to IV fosfomycin being used in combination with a host of other antimicrobial agents against various deep-seated infections due to resistant gram-positive and gram-negative pathogens.[36,37] Del Rio and "FOSIMI" investigators conducted an open-label prospective trial of IV fosfomycin plus imipenem for complicated bacteremia and endocarditis caused by MRSA. Subjects were 16 adults across three teaching hospitals in Barcelona and Madrid from 2001–10, 14 with persistence of MRSA in blood; early subjects had fosfomycin 2 g every 6 hours plus imipenem 1g every 6 hours added to their initial regimen of vancomycin, whereas after 2006 the fosfomycin-imipenem regimen replaced initial therapy of either vancomycin or daptomycin, 6 to 10 mg/kg body weight every 24 hours. Investigators found all patients to have negative blood cultures at 72 hours after initial dosing of fosfomycin-imipenem (a primary end point) without recurrence, with only one death attributed to MRSA.[38] In contrast, studies using other therapies, including combination therapy, have shown a mean clearance of complicated MRSA bacteremia to range from 6 to more than 8 days.[39,40] The clinical success rate at TOC (45 days after EOT) was deemed to be 69% and therapy considered safe, although several patients manifested hypernatremia, and one death was attributed to sodium overload.

Regarding highly resistant gram-negative infections, an in vitro study by Falagas and colleagues[41] demonstrated activity of fosfomycin against ESBL- and MBL-producing isolates of *K. pneumoniae*. A more recent in vitro study of ZTI-01 activity against 50 clinical CRE isolates also used existing oral fosfomycin breakpoints, with an MIC >64 µg/ mL defining resistance. A majority of isolates (42) were *K. pneumoniae* largely consisting of a variety of KPC, but also a variety of strains having OXA, VIM-1, NDM-1 and NDM-6. Also noted were that 36 (72%) and 20 (40%) isolates possessed *ompK*35 and *ompK*36 porin mutations, respectively. Forty-seven (94%) of isolates demonstrated fosfomycin susceptibility, including susceptibility to 14 isolates resistant to ceftazidime-avibactam (Avycaz). Three isolates demonstrated resistance to fosfomycin via modifying enzymes—1 fosA2, 1 fosA3, and another undetermined.[42]

In conclusion, attractive attributes are IV fosfomycin's broad activity against resistant gram-negative and gram-positive pathogens, as well as additive or synergistic properties when combined with a host of other agents from antimicrobial classes such as β-lactams, carbapenems, lipoglycopeptides, AG, polypeptides, and glycylcyclines. It would also find use in patients with intolerance or allergies to some of these more often-used antimicrobials.

Also, despite a route of elimination that is primarily renal excretion, the drug is not associated with overt nephrotoxic effects. In contrast, fosfomycin for severe resistant infections should be given with other antibacterials and not as monotherapy.[43] Monitoring this novel antibacterial in parenteral form should be subject to further close observation as early studies had small sample sizes. Dosing should be reduced in the presence of diminished renal function, and higher doses have been associated with bradycardia.[44] Each 1 g of fosfomycin contains 330 mg of sodium, so even reduced doses can be burdensome, particularly among fragile populations with cardiac, renal, or hepatic failure. Other noted AEs include hypocalcemia, hypokalemia, and phlebitis.

Omadacycline (PTK 0796, Nuzyra)

Omadacycline (Paratek Pharmaceuticals, Boston, MA) is among the aminomethylcyclines derived from the core structure of tetracycline that are protein synthesis inhibitors and represent a novel class of antibiotics with potent in vitro activity against tetracycline-resistant organisms. This first-in-class semisynthetic agent is available in IV and oral formulations; in February 2018 an NDA was submitted to the FDA for omadacycline for the treatment of community-acquired bacterial pneumonia (CABP) and ABSSSI. These indications received a favorable FDA Advisory Committee recommendation for approval in late August 2018, and a followed with FDA approval in October 2018. The MIC range against MRSA isolates, which included several vancomycin-resistant *S. aureus* and vancomycin-intermediate *S. aureus* strains, was 0.06 to 2 µg/mL.[45] Against *Legionella* spp., the MIC was 0.25 µg/mL.[46] In vitro activity also includes vancomycin-resistant enterococci and some resistant gram-negative pathogens, including *A. baumannii* (MIC, 8 µg/mL).[47,48] An in vitro study of PTK 0796 and comparator agents assessed activity against a total of 1024 respiratory isolates, including *S. pneumoniae, H. influenzae*, and *M. catarrhalis,* from European Union centers in 2011. The investigators concluded that omadacycline's activity was relatively unaffected by penicillin or tetracycline susceptibility patterns with demonstrably potent activity against these key respiratory pathogens and that pneumonia studies are warranted.[49]

Additional in vitro susceptibility testing of omadacycline was performed against reference strains and clinical isolates from the United States and China of *Mycoplasma pneumoniae* and *Mycoplasma hominis,* as well as *Ureaplasma parvum* and *Ureaplasma urealyticum*. Comparator agents were tetracycline, doxycycline, azithromycin; moxifloxacin with clindamycin was substituted for azithromycin for *M. hominis* isolates. An MIC_{90} value of 0.063 µg/mL for omadacycline was the lowest among all drugs tested against *M. hominis* with all omadacycline MICs <0.125 µg/mL, including tetracycline-resistant strains. Azithromycin had the highest potency against *M. pneumoniae*, but the omadacycline MIC_{90} was 0.25 µg/mL and 0.125 µg/mL against 10 strains having high-level macrolide resistance with azithromycin MICs >16 µg/mL. Omadacycline was less potent against *Ureaplasma* spp. although its activity was again not lessened by the presence of quinolone or high-level tetracycline resistance. With consistency to an earlier study, the authors concluded omadacycline demonstrated in vitro bacteriostatic activity against the organisms tested.[50,51]

Omadacycline given 100 mg IV every 12 hours for two doses, followed by three doses every 24 hours demonstrated epithelial lining fluid (ELF) and alveolar macrophage (AM) concentrations 1.5 and 25 times greater, respectively, than plasma among 41 healthy subjects.[52]

A phase III randomized, double-blind, multicenter trial across 86 sites termed OPTIC (Omadacycline for Pneumonia Treatment in the Community), compared omadacycline to moxifloxacin in adults with CABP. Omadacycline was loaded IV, 100 mg every 12 hours (two doses), followed by 100 mg every 24 hours, whereas moxifloxacin 400 mg was administered every 24 hours. After 3 days, a possible step-down to oral drug was offered, omadacycline 300 mg or moxifloxacin 400 mg, both every 24 hours for a total treatment duration of 7 to 14 days. A total of 770 subjects were randomized 1:1, and stratification by PORT (Pneumonia Outcomes Research Team) risk scores II to IV was even, both arms with a ≤15% limitation of PORT II score and a limit of ≤25% randomized subjects receiving a prior antibiotic. Subjects were predominantly white, having a mean body mass index (BMI) of 27, with 42% age older than 65 years, another 20% older than 75 years, all evenly matched. Among a total of 685 clinically evaluable subjects clinical success at early clinical response (ECR, days 3–5) 81.1% to 82.7%, EOT (days 7–14) 87.6% to 85.1%, and posttreatment evaluation (PTE, 5–10 days after last dose of drug) 92.9% to 90.4%, omadacycline to moxifloxacin, respectively. Clinical success was also similar against a spectrum of gram-positive, gram-negative, and atypical respiratory baseline pathogens isolated from microbiologically modified intent-to-treat subjects. Safety profiles were also similar, but for diarrhea, which was markedly higher for moxifloxacin and *Clostridioides difficile* (formerly *Clostridium difficile*) infection, all eight cases among the moxifloxacin arm.[53]

The OASIS (Organization to Assess Strategies in Ischemic Syndromes) 1 and OASIS 2 trials were large, randomized, double-blinded multicenter phase III studies comparing omadacycline with omadacycline versus LZD, whereas OASIS 2 compared only oral formulations. Noninferiority for efficacy for omadacycline to LZD and comparable safety profiles were demonstrated in each trial.[54] From OASIS I, an analysis of a subgroup of subjects having a high BMI (≥ 25 kg/m^2) or diabetes mellitus was undertaken to assess the efficacy and safety of the omadacycline dosing schema of 100 mg IV and 300 mg oral dosing. Seventy-nine percent of subjects in either the omadacycline or LZD cohorts had ABSSSI deemed due to IV drug use, 66% of subjects having *S. aureus*, the most common baseline pathogen. As a composite of normal BMI and high BMI subjects, the rate of infusion site extravasation was noted to be

1.5-fold higher among omadacycline subjects. Investigators concluded that IV to oral step-down therapy of omadacycline was efficacious and well tolerated in treating ABSSSI regardless of BMI or diabetic status, with similar outcomes compared with LZD at ECR and PTE. Dose adjustment of omadacycline was not needed.[55]

Omadacycline showed good in vitro activity against common Enterobacteriaceae responsible for UTIs.[56] Not yet determined is whether it would be a good antibacterial to treat UTIs, with 27% of an IV-administered omadacycline dose being eliminated in the urine of healthy subjects. What is known is that overall clearance and volume of distribution were similar among healthy subjects and subjects having end-stage renal disease; thus omadacycline dose adjustment is not required for subjects with renal impairment or those on hemodialysis.[57] As a tetracycline it would be anticipated to have prominent warnings regarding its use among pregnant or lactating women. Similar to tigecycline and eravacycline (discussed later) and the tetracycline class, omadacycline possesses little to no activity against *P. aeruginosa*. Data on activity against *Vibrio* spp., *Aeromonas* spp., and other halophilic gram-negative rods and the *Rickettsiaceae* are also lacking.

In conclusion, the IV and oral dosage forms present an advantage to omadacycline for uniform, step-down therapy of CABP and ABSSSI when needed. Omadacycline displays very good activity against key gram-positive, gram-negative, and atypical respiratory pathogens, including those displaying tetracycline resistance; susceptible organisms also include MRSA. It presents an excellent option for CABP or ABSSSI patients having a penicillin allergy or intolerance to "mainstay" community or hospital antibacterial regimens, including the fluoroquinolones, as well as lessening selective pressures of those regimens. Postmarketing surveillance should include close observation of omadacycline regimens that solely use the oral formulation. In these instances it appears a loading dose of 450 mg for the first 2 days of therapy will initiate the oral regimen, curtailing to remaining daily doses of 300 mg. Pharmacovigilance regarding GI tolerance, patient adherence, and outcomes seems warranted.

Eravacycline (TP-434, Xerava)

Eravacycline (Tetraphase Pharmaceuticals, Watertown, MA) is a fluorinated tetracycline derivative considered to be a novel fluorocycline. Owing to modifications at the C-7 and C-9 positions of its tetracycline core, eravacycline possesses broad-spectrum antimicrobial activity and demonstrates remarkable potency to pathogens, even those with tetracycline-specific efflux and ribosomal protection and inactivation.[58] The C-9 modification also appears to confer oral activity to this compound.[59]

Eravacycline has demonstrated in vitro activity against uropathogens responsible for cUTI. Within 8 hours of the first IV dose of eravacycline, 1.5 mg/kg body weight, urinary concentrations of the drug were shown to be 4- to 14-fold higher than eravacycline's MIC_{90} (0.5 μg/mL–2 μg/mL) to many common cUTI pathogens,[60] although it is not active against *P. aeruginosa*. However, in two phase III clinical trials IGNITE-2 (Investigating Gram-Negative Infections Treated With Eravacycline 2) and IGNITE-3, eravacycline as once-daily IVPB therapy with step-down to oral eravacycline (IGNITE-2), and later in IGNITE-3, to oral levofloxacin, respectively, failed to achieve statistical noninferiority for efficacy end points compared with IV levofloxacin to oral levofloxacin (IGNITE-2) or ertapenem to oral levofloxacin (IGNITE-3) for the treatment of patients with cUTI, including AP. Although well tolerated at the 200-mg every-12-hours oral dose used, Tetraphase has discontinued the oral formulation of eravacycline.

IGNITE-1 was the first of two randomized, controlled, double-blinded, prospective studies in the treatment of cIAI designed to assess the efficacy and safety of the drug. Eravacycline was dosed IV 1 mg/kg body weight every 12 hours and compared with ertapenem, dosed IV 1 g every 24 hours. Eravacycline achieved high cure rates in patients having gram-positive aerobic baseline pathogens, as well as those with infections caused by ESBL-producing Enterobacteriaceae, including a lone carbapenemase-resistant isolate; it achieved 100% clinical cure against a variety of drug-resistant *Acinetobacter* spp. Clinical cure was also high among patients, accounting for 70 isolates of *B. fragilis* and *Bacteroides thetaiotaomicron* (88.6% and 88.5%, respectively) but only 68.4% for *Bacteroides ovatus*.[61]

TABLE 36.3 In Vitro Susceptibility of TP-434 and Comparators to *Escherichia coli* DH10B–Expressing Major Tetracycline-Resistance Genes (MIC in μg/mL)

ANTIBIOTIC	*lacZ*	*tet(M)*	*tet(K)*	*tet(A)*	*tet(B)*	*tet(X)*
Eravacycline	0.063	0.063	0.031	0.25	0.063	4
Tigecycline	0.063	0.13	0.063	1	0.063	2
Doxycycline	2	64	4	32	32	16
Minocycline	0.5	64	1	8	16	4
Tetracycline	2	128	128	>128	>128	128
Ceftriaxone	0.063	0.13	0.063	0.13	0.13	0.13

MIC, Minimal inhibitory concentration.
Modified from Grossman TH, Starosta AL, Fyfe C, et al. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. Antimicrob Agents Chemother. *2012;56:2559–2664.*

Eravacycline demonstrated an MIC_{90} of ≤0.5 μg/mL to 445 isolates of *E. coli,* of which 127 (29%) showed intermediate resistance or resistance to third-generation cephalosporins. Among these were a broad range of ESBL- and carbapenemase-producing isolates. The drug exhibited similar potency against good numbers of fluoroquinolone-, AG-, and MDR-resistant (three or more antibacterial classes) and tetracycline-resistant isolates. It performed equally well, besting all comparators except colistin, against 52 isolates of *A. baumannii,* with exquisite activity as low as 0.016 μg/mL (lowest) to carbapenem-intermediate and carbapenem-resistant isolates, as well as fluoroquinolone- and AG-resistant strains.[62] In another in vitro study examining eravacycline activity against major tetracycline resistance mechanisms, it exhibited a fourfold greater potency than tigecycline against a clinical strain of *E. coli* DH10B expressing a widespread tetracycline efflux pump (TetA),[58] as seen in Table 36.3**.** The TetA mechanism predominates in Enterobacteriaceae and certain other pathogens, such as *Vibrio* spp., *P. aeruginosa,* and *Aeromonas* spp. A later in vitro study of activity against Enterobacteriaceae demonstrated eravacycline's potency against ESBL-, KPC-, NDM- and OXA-producing *Klebsiella* spp.; eravacycline's $MIC_{50/90}$ was 0.5/2 μg/mL, including AG- and fluoroquinolone-nonsusceptible isolates. The $MIC_{50/90}$ was 2/8 μg/mL against tigecycline-resistant *Klebsiella*.[62,63] Eravacycline is known to not have meaningful activity against *Pseudomonas* spp.

ELF and AM achieve higher eravacycline concentrations compared with plasma by 6- and 50-fold, respectively, in healthy subjects.[64] The penetration into AM speaks to a potential advantage in treating intracellular organisms such as *Legionella* spp., whereas eravacycline's ELF penetration could indicate optimal activity against extracellular organisms, such as *S. pneumoniae*, *S. aureus,* and *Acinetobacter* spp.

The drug demonstrates potent activity against *S. aureus*, regardless of methicillin susceptibility and *Enterococcus* spp. independent of vancomycin or LZD susceptibility or daptomycin nonsusceptibility. The $MIC_{50/90}$ of eravacycline versus comparators demonstrated excellent in vitro activity to a number of anaerobic pathogens, including *B. fragilis, C. difficile*, and *Finegoldia magna,* although activity against species of non-*fragilis Bacteroides* showed a wider range of MIC values. In vitro activity against several clinically important oropharyngeal anaerobes, including *Peptostreptococcus* spp. and *Fusobacteria* spp., appears excellent.[62]

Like tigecycline, it appears that GI side effects, such as nausea and vomiting, reported at 3.3% and 2.2% of study subjects, respectively, are among the most frequent.

From eravacycline's two phase III cIAI trials (IGNITE 1 and IGNITE 4, compared with ertapenem and meropenem, respectively) the drug's FDA-labeled dosing is as twice-daily IV therapy for the treatment of cIAI, including resistant and MDR pathogens susceptible to eravacycline. As a tetracycline its labeling includes prominent warnings regarding its use among children up to age 8 years and pregnant or lactating women. Eravacycline's PK/PD profile coupled with its broad spectrum of activity, including *Legionella* spp., suggest it might be used in the treatment or studies of hospital-acquired and ventilator-associated

pneumonias. The company also has TP-271, another tetracycline derivative, in oral and IV formulations finishing phase I trials aimed at CABP.

In conclusion, in late August 2018 twice-daily IV Xerava received FDA approval for the treatment of cIAI, including resistant and MDROs susceptible to eravacycline, ESBL-producing strains, and CRE. Somewhat unique to its labeling, the FDA has allowed the statement that eravacycline demonstrated in vitro bactericidal activity against certain strains of *E. coli* and *K. pneumoniae.* Also, as a limitation of use, Xerava's labeling specifies the drug is not indicated for the treatment of cUTI. The oral dose formulation program for oral eravacycline has been discontinued, so its use will be chiefly relegated to hospital floor and ICU settings. Xerava displays broad activity against gram-negative and gram-positive MDRO pathogens, including broad anaerobe activity. It appears that the manufacturer (Tetraphase) will forego formal studies of use of eravacycline for pulmonary infection, instead seeking to advance other synthetic tetracycline moieties for potential pulmonary indications. More detailed PK/PD data on the disposition of eravacycline in blood and penetration into various tissue sites is needed to aid clinician certainty in prescribing this antibacterial for patients having suspected or documented MDRO infections. Regardless of patient allergy status, eravacycline's prescribing could lessen selective pressures by sparing prescribing of antibacterial classes such as β-lactams/carbapenems and quinolones. It would not require dose adjustment for patients having diminished renal function.

Last, as a tetracycline derivative, if supported by PK/PD data for a once-daily dosing schema achieving sufficient bone concentrations, eravacycline could have potential utility for off-label empirical or targeted therapy in osteomyelitis.

Lefamulin (BC-3781)

Lefamulin (Nabriva Therapeutics, Dublin, Ireland) is a novel systemic pleuromutilin antimicrobial inhibiting bacterial protein synthesis by interaction with 23S ribosomal RNA of the 50S bacterial ribosome subunit. Until BC-3781, pleuromutilins, known since the 1950s, have been relegated to veterinary medicine and topical use in humans (retapamulin, Altargo, Altabax; Glaxo-Smith Kline, Philadelphia, PA) due to toxicity. This systemic pleuromutilin antibacterial possesses excellent bioavailability, and both IV and oral formulations are in clinical trials for CABP (phase III completed) and ABSSSI (late phase II).

Lefamulin possesses potent in vitro activity against common gram-positive skin organisms, including *S. aureus* (methicillin-sensitive *S. aureus* [MSSA] and MRSA), coagulase-negative *Staphylococcus* spp., *Streptococcus agalactiae*, and *Streptococcus pyogenes*. It also exhibits in vitro activity against a broad array of gram-positive and gram-negative community respiratory pathogens, including *S. pneumoniae*, *Moraxella catarrhalis,* and *Haemophilus influenzae,* as well as atypical bacteria—*Legionella pneumophila, C. pneumonia*e, and *M. pneumoniae*. An in vitro study of lefamulin activity against 822 isolates of *S. pneumoniae* collected from 58 hospitals across nine US census regions showed an overall $MIC_{50/90}$ of 0.125 μg/mL and 0.25 μg/mL to (1) common serotypes, (2) isolates displaying ceftriaxone or erythromycin nonsusceptibility, or (3) MDR serotypes defined as resistant to three or more antimicrobial classes.[65] Compared with moxifloxacin, azithromycin, erythromycin, tetracycline, and doxycycline against small subsets of macrolide-sensitive and -resistant strains of *M. pneumoniae* from Europe, China, and the United States, lefamulin demonstrated potent bactericidal activity to all and with an MIC_{90} of 0.002 μg/mL to resistant strains.[66]

A small study of 12 healthy male subjects examined lefamulin concentrations in plasma, skeletal muscle tissue, subcutaneous adipose tissue, and pulmonary ELF after a single IV 150-mg dose administered in 400 mL normal saline over 1 hour. Findings were notable plasma levels with rapid and good penetration into skeletal muscle and adipose tissues and also an ELF concentration 5.7-fold higher than free plasma levels of lefamulin. Investigators postulated that, like macrolides, lefamulin as a P-glycoprotein substrate may be actively transported into ELF.[67]

At 20 US centers a phase II study compared 100 mg or 150 mg lefamulin or 1 g vancomycin, each given IVPB every 12 hours for 5 to 14 days, for ABSSSI. Patients (n = 210) were 18 years or older and randomized 1:1:1. ABSSSI characteristics for primary infection type and lesion size were similar, as were other baseline characteristics for age, underlying diabetes mellitus, body weight, and concomitant bacteremia. Rates of clinical success for MSSA and MRSA were similar among all three arms. Clinical success rates among clinically evaluable subjects was similar: 90%, lefamulin 100 mg; 88.9%, lefamulin 150 mg; and 92.2%, vancomycin 1 g. The reduction of lesion size at 72 hours, the first 5 days of therapy, and at EOT and TOC were similar among all three arms. The clinical success rate was also considered equivalent by various patient subgroups and baseline pathogens, including Panton-Valentine leukocidin–positive MRSA and USA300 MRSA. The mean duration of therapy was approximately 7 days for all three groups, with a higher rate of drug-related AE in the vancomycin arm. Among lefamulin subjects the most frequent AEs were headache, nausea, and diarrhea, although local infusion site reactions and phlebitis were more frequent compared with vancomycin. There were no occurrences of *C. difficile* infection. Small increases in QT fixed correction factor (QTcF) interval were noted, although no subject had a QTcF >480 ms, nor increase in QTcF >60 ms from baseline. This was the first study of a systemic pleuromutilin used for ABSSSI and should advance to phase III studies based on FDA stance of the LEAP (Lefamulin Evaluation Against Pneumonia) trials for CABP.[68]

The phase III LEAP I trial was a global multicenter, double-blind, randomized, controlled trial evaluating lefamulin versus moxifloxacin with or without adjunctive LZD in adult subjects with moderate-to-severe CABP. Both antibacterials were administered IVPB, with transition to oral lefamulin or moxifloxacin ± LZD. There were 551 subjects—275 in the lefamulin arms and 276 in the moxifloxacin arm—and were evenly matched regarding PORT scores, with the majority of subjects falling into PORT classes III (lefamulin, n = 196; moxifloxacin, n = 201) and IV (lefamulin, n = 76; moxifloxacin, n = 70). Among modified intent-to-treat subjects, rates of ECR were reported similar among *S. pneumoniae* and *S. aureus* infections.[69]

Regarding safety and tolerability, rates of TEAEs leading to study drug discontinuation were 2.9% for lefamulin versus 4.4% for moxifloxacin with or without LZD. Notable AEs in >2% of patients receiving the study drug (lefamulin vs. moxifloxacin with or without LZD, respectively) were hypokalemia (2.9% vs. 2.2%), nausea (2.9% vs. 2.2%), insomnia (2.9% vs. 1.8%), infusion site pain (2.9% vs. 0%), and infusion site phlebitis (2.2% vs. 1.1%). One subject in each arm displayed an increase in absolute QT interval to >500 ms.

In conclusion, to date BC-3781 has no cross-resistance with other major classes of antibacterials and shows good activity against numerous pathogens, including drug-resistant strains responsible for CABP and ABSSSI. The phase III trial of lefamulin for CABP, LEAP 2 completed enrollment in late 2017, and mid-2018 analysis of results regarding safety and efficacy were also positive. Lefamulin will be initially submitted for FDA and EMA market approval, offering a novel IV/oral antibacterial for mild-to-severe CABP. Relating to previous patient exposure, allergies or intolerance, and antimicrobial stewardship, lefamulin's potential approval provides antibacterial monotherapy with oral step-down, if needed, with little consideration of cross-resistance and avoidance of later-generation cephalosporins and quinolones for CABP therapy.

Iclaprim

Iclaprim (Motif Biosciences, New York, NY) is primarily active against gram-positive organisms. Like trimethoprim, to which it bears some structural similarity, iclaprim inhibits bacterial dihydrofolate reductase. Earlier the drug was branded Mersarex by Arpida Pharmaceuticals (Reinach, Switzerland) and applications to the FDA (ASSIST 1 and 2) and EMA for complicated skin and skin-structure infections were rejected and withdrawn in 2009. Chief concerns were safety owing to QTc prolongation and concomitant antibiotic use before study entry, which could have obscured efficacy.[70] However, in 2015 Motif Biosciences embarked on reexamination of iclaprim, and in late 2017 the FDA granted the drug orphan status for the treatment of *S. aureus* pulmonary infections in patients with cystic fibrosis.[71] With that and PK data pulled from 470 ASSIST I patients, Monte Carlo modeling sought to determine optimal efficacy dosing for MRSA while avoiding serum concentrations exceeding 800 ng/mL, this iclaprim concentration associated with AEs. It was determined in contrast to weight-based dosing used in the ASSIST trials, a fixed dose of iclaprim, 80 mg IVPB over 2 hours every 12 hours could be used for ABSSSI trials.[72]

With clinical breakpoints not yet established, an MIC ≤ 1 μg/mL for MSSA and MRSA was proposed for an in vitro study activity of iclaprim against MRSA nonsusceptible to daptomycin, LZD, and vancomycin. These latter three antibacterials have indications for ABSSSIs and LZD-vancomycin for nosocomial pneumonia. In a 2017 study with a small number of MRSA isolates, iclaprim demonstrated bactericidal activity against a majority of nonsusceptible daptomycin, LZD, and vancomycin organisms: 71%, 100%, and 67%, respectively.[73] This perhaps lends validity to sustained activity of the drug demonstrated in a 2009 in vitro study of 5937 European and US gram-positive clinical isolates from 2004–06. Iclaprim then exhibited bactericidal activity against all MRSA strains and potent activity against β-hemolytic *Streptococcus* spp. and *E. faecalis*.[74]

With an NDA expected to be filed in early 2018 (indication: ABSSSI), iclaprim recently completed a phase III randomized, double-blind, multicenter trial (REVIVE I) of ABSSSI in 598 subjects due to gram-positive organisms. Per recent FDA guidelines, a primary end point was ECR, defined as a ≥20% reduction in lesion size within an early time point of 48 to 72 hours, comparing fixed-dose 80 mg iclaprim versus vancomycin 15 mg/kg, both given IVPB every 12 hours for 5 to 14 days, duration based upon investigator discretion. Median lesion size was approximately 330 cm^2 in each arm, with primary end point of ECRs similar: 80.9% (241/298) iclaprim to 81% (243/300) vancomycin. Clinical cure rates, determined 7 to 14 days after EOT, were also similar: 83% (248/298) to 87% (262/300) for iclaprim and vancomycin, respectively. Organisms recovered were predominantly MSSA and MRSA, followed by β-hemolytic *Streptococcus,* evenly matched in each arm as was an approximate 5% rate of concomitant bacteremia. Wound definition (e.g., major cutaneous abscess, cellulitis/erysipelas, wound infection) and determination of severity were also well matched. Compared with vancomycin, a higher incidence of headache, nausea, and fatigue was noted among subjects receiving iclaprim, with similar rates of study drug–related TEAEs. TEAEs leading to study drug discontinuation was 2.7% for iclaprim compared with 4.4% for vancomycin. One patient in the iclaprim group experienced QTc intervals >500 ms and increased by 60 ms compared with baseline. Iclaprim discontinuation resulted in a return to baseline values.[75]

Iclaprim has received QIDP status for ABSSSI and for HABP. A recent (2017) manuscript of a shortened phase II trial enrolling 70 subjects from 2007 through early 2009 compared two weight-based dosages of iclaprim to vancomycin, randomized 1:1:1, for suspected or confirmed nosocomial pneumonia due to gram-positive pathogens.[76] With comparable rates of clinical cure and safety profile to vancomycin, there are plans to bring iclaprim to phase III trials, coined INSPIRE (*I*claprim for *N*o*S*ocomial *P*neumon*I*a g*R*am-positive pathog*E*ns), of HABP including VABP. An earlier 2007 study of single-dose iclaprim pulmonary distribution did demonstrate ELF and AM concentrations 20- and 40-fold greater, respectively, than plasma.[77]

It appears iclaprim spares patients substantial renal toxicity and spares clinicians the need for renal dose adjustment, but a 50% dose reduction was recommended for patients having moderate hepatic impairment (Child-Pugh class B) in earlier studies using weight-based dosing (EMA letter). Whether or not 80-mg fixed-dosing would require adjustment in this population is uncertain, as well as whether or not it would achieve suitable target attainment activities against pathogens causing infection in sites other than ABSSSI. As a singular entity not combined with a sulfur-containing agent, as is trimethoprim-sulfamethoxazole, iclaprim would avoid issues of patients having a sulfa allergy; however, unlike trimethoprim it is not available in oral formulation.

In conclusion, iclaprim is a gram-positive, active, oral antibacterial demonstrating very good activity against β-hemolytic streptococci and *S. aureus,* including MRSA. It has variable activity against the enterococci, as expected exhibiting greater activity against *E. faecalis* isolates than *E. faecium*, and also of US origin versus Europe, in one in vitro analysis.[74] Dosing adjustments do not appear necessary for diminished renal function but would possibly be recommended in the presence of moderate hepatic dysfunction. As mentioned, iclaprim lacks an oral formulation. It has potential as monotherapy or step-down from other broader parenteral therapies for ABSSSI and for this indication was granted FDA priority review and a PDUFA date of February 13, 2019. However, in February 2019, Motif Bio received an FDA Complete Response Letter holding up potential approval requesting additional data for evaluation of hepatotoxicity in study patients. Iclaprim also demonstrates excellent penetration into the ELF and AMs, so it has potential utility in various pneumonias, given its gram-positive spectrum. However, for indications other than ABSSSI, further PK/PD study is needed regarding dosing demonstrating efficacy and an acceptable profile of adverse drug events.

OVERALL CONCLUSIONS

The antibacterial agents outlined in this chapter appear most promising, with several agents receiving approval for use in the United States only very recently. The present challenge in finding effective treatment for locally invasive or systemic disease caused by MDROs has reached near-alarming concerns. *E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa,* and *Enterobacter* spp. were abbreviated as "ESKAPE" to identify problem pathogens that elude treatment with commonly used antibiotics. Economic incentives for industry-sponsored new drug development (Table 36.4) are promoted by a relative ease in gaining market entry, as regulatory agencies recognize limited available

TABLE 36.4 Other Novel Antibacterial Drugs in Advanced Stages of Development

Debio-1452 (formerly AFN-1252, Affinium); Debiopharm Group	Late phase-II (ABSSSIs)	Novel agent, inhibits enoyl reductase (FabI-inhibitor). Inhibits bacterial fatty-acid biosynthesis, targeting the FabI enzyme in staphylococci (SaFabI). Recent findings show Debio-1452 binds to the BpmFabI enzyme, inhibiting growth of *Burkholderia pseudomallei*. Other late-generation FabIs in very early development show inhibitory activity against *Acinetobacter baumannii* and demonstrable synergy with colistin	Multicenter trials in United States and Canada for targeted oral therapy of ABSSSIs due to staphylococci (MSSA and MRSA). Inactive against streptococci, enterococci, and Enterobacteriaceae. In United States, recent (completed 2016) 25-site, double-blind, controlled trial, randomized 1:1:1 (*N* = 330), two separate doses of IV/PO Debio-1452 to IV vancomycin/oral linezolid (V/LZD) for ABSSSI due to staphylococci, including MRSA. Noninferiority to V/LZD was demonstrated in both arms across patient status (cellulitis and diabetes mellitus). Rates of early clinical response (48–72 h) were 94.6% and 90.1% for Debio-1452 to 91.1% V/LZD. Debio-1452 also found safe and well tolerated
Solithromycin (formerly CEM 101); Melinta Therapeutics	III (CABP)	A novel fluoroketolide, a fourth-generation macrolide agent demonstrating activity to pathogens resistant to earlier-generation macrolide agents, such as erythromycin, azithromycin—first- and second-generation agents, respectively. Binds at three sites of 50S subunit of the bacterial ribosome, compared with current macrolide agents binding at one site and has IV and PO formulations; blocks protein synthesis, preventing bacterial growth and reproduction	Met efficacy in phase III trials for CABP in adults. However, an FDA complete response letter relative to both PO and IV formulations for safety regarding hepatotoxicity requested a large-subject supplemental safety study and a comprehensive pharmacovigilance program. In 2017 did not meet noninferiority end points in a phase III trial (SOLITAIRE-U) comparing an oral 1-g dose of solithromycin against parenteral ceftriaxone plus oral azithromycin in uncomplicated gonorrhea with or without *Chlamydia* infection. Status of return to studies remains uncertain

TABLE 36.4 Other Novel Antibacterial Drugs in Advanced Stages of Development—cont'd

Sulopenem (IV and PF-03709270, sulopenem etzadroxil); Iterum Therapeutics	II complete (CABP)	Carbapenem antibacterial. Inhibits cell wall synthesis by binding penicillin-binding proteins. IV formulation and a potential first-in-class oral agent as prodrug	QIDP status granted for uUTI, cUTI, and cIAI. Active against MDROs. Anticipate starting phase III trials of cUTI mid-2018
Cadazolid; Actelion/Janssen	III (*Clostridioides difficile [formerly Clostridiium difficile]*–associated diarrhea)	Novel chimeric quinolinyl-oxazolidinone, having structural elements of both quinolones and oxazolidinones. In vitro testing of resistance development demonstrated cadazolid activity against moxifloxacin-resistant strains	Two phase III double-blinded, randomized, controlled trials (IMPACT 1 and 2, *n* = 1263 adult subjects) comparing cadazolid 250 mg PO bid vs. vancomycin 125 mg PO qid in patients with *C. difficile* infection. Both trials demonstrated safety and tolerability of cadazolid. However, although IMPACT 1 met its primary end point of clinical cure at end of therapy, IMPACT 2 failed to meet the primary end point. A study of cadazolid in pediatric subjects (NCT03105479) is ongoing. Resumption of additional adult phase III trials (???)
POL7080/murepavadin; Polyphor	II (VABP), or nosocomial pneumonias due to *Pseudomonas aeruginosa*). Planned phase III trials (NCT02096315) for early 2018	OMPTA. Pathogen-specific peptidomimetic binding of lipopolysaccharide transport protein D inhibits its export and ultimately causes cell death. A pathogen-specific antibacterial (*Pseudomonas* spp.) with no activity against Enterobacteriaceae or gram-positive pathogens	In an open-label multicenter trial of VABP likely due to *P. aeruginosa* in 25 subjects, POL7080, 2. 5 mg/kg IVPB q8h, was added to standard-of-care therapy for 10–14 days. Preliminary results in 12 subjects having confirmed *P. aeruginosa* at baseline (5 with MDR *P. aeruginosa*) showed 91% rate of clinical cure with 9% all-cause mortality at day 28

ABSSSI, Acute bacterial skin, skin-structure infection; *bid,* twice daily; *BpmFabI, Burkholderia pseudomallei* enoyl-acyl carrier protein reductase; *CABP,* community-acquired bacterial pneumonia; *cIAI,* complicated intraabdominal infections; *cUTI,* complicated urinary tract infection; *FabI,* an enoyl-acyl carrier protein reductase; *FDA,* US Food and Drug Administration; *IV,* intravenously; *IVPB,* intravenous piggyback; *MDR,* multidrug resistant; *MDRO,* multidrug-resistant organism; *MRSA,* methicillin-resistant *Staphylococcus aureus; MSSA,* methicillin-sensitive *S. aureus; OMPTA,* outer membrane protein targeting antibiotic; *PO,* orally; *qid,* once per day; *QIDP,* Qualified Infectious Disease Product; *SaFabI, S. aureus* enoyl-acyl carrier protein reductase; *uUTI,* uncomplicated urinary tract infection; *VABP,* ventilator-associated bacterial pneumonia; *VILZD,* vancomycin/linezolid (combination).

options for cure of conditions such as cancer.[78] It is estimated currently that 500 million to 1 billion dollars are spent in the launching of a new antimicrobial drug for clinical use; this includes costs for biochemical research, preclinical development, and mandatory clinical trials.[79,80] New entries to the market should be shepherded with the best intentions for antimicrobial stewardship and cautious pharmacovigilance, especially to monitor for AEs and toxicities that become apparent during the postmarketing period. As with any prescription medication, time will allow for the distinction of the most useful of these antibacterials. To be considered are all the PK/PD characteristics of the new agents across broad clinical scenarios. These would include the likelihood of multiple off-label indications, application for and receipt of newly labeled indications, patent strategies, and ease of provider and patient use in the face of observations regarding outcomes, safety, and drug interactions.

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References

1. Boucher H, Talbot G, Bradley J, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:1–12.
2. Boucher HW, Talbot GH, Benjamin DK, et al. 10 × '20 progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:1685–1694.
3. Federal Register. Establishing a List of Qualifying Pathogens Under the Food and Drug Administration Safety and Innovation Act. https://www.federalregister.gov/documents/2014/06/05/2014-13023/establishing-a-list-of-qualifying-pathogens-under-the-food-and-drug-administration-safety-and. Accessed February 27, 2018.
4. Okeke IN, Laxminarayan R, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis*. 2005;5:481–493.
5. Aggen JB, Armstrong AS, Goldblum AA, et al. Synthesis and spectrum of the neoglycoside ACHN-490. *Antimicrob Agents Chemother*. 2010;54:4636–4642.
6. Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2184 adult patients. *Antimicrob Agents Chemother*. 1995;39:650–655.
7. Drusano GL, Ambrose PG, Bhavnanni SM, et al. Back to the future: using aminoglycosides again and how to dose them optimally. *Clin Infect Dis*. 2007;45:753–760.
8. Endimiani A, Hujer KM, Hujer AM, et al. ACHN-490, a neoglycoside with potent in vitro activity against multidrug-resistant *Klebsiella pneumonia* isolates. *Antimicrob Agents Chemother*. 2009;53:4504–4507.
9. Connolly LE, Riddle V, Cebrik D, et al. Efficacy and safety of plazomicin compared with levofloxacin in the treatment of complicated urinary tract infection and acute pyelonephritis: a multicenter, randomized, double-blind, phase 2 study. *Antimicrob Agents Chemother*. 2018;62:pii:e01989-17.
10. Landman D, Babu E, Shah N, et al. Activity of a novel aminoglycoside, ACHN-490, against clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* from New York City. *J Antimicrob Chemother*. 2011;66:332–334.
11. Pankuch GA, Lin G, Kubo A, et al. Activity of ACHN-90 tested alone or in combination with other agents against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2011;55:2463–2465.
12. Tenover FC, Tickler I, Armstrong E, et al. Activity of ACHN-490 against methicillin-resistant *Staphylococcus aureus* (MRSA) isolates from patients in US hospitals. *Int J Antimicrob Agents*. 2011;38:352–354.
13. Heine HS, Chuvala L, Riggins R, et al. Efficacy of plazomicin against *Yersinia pestis* in a murine-aerosol challenge late-treatment model. Proceedings of the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy 2012, San Francisco, Sept 9-12; B-1302, session 164.
14. McKinnell JA, Connolly LE, Puskin R, et al. Improved outcomes with plazomicin compared with colistin in patients with bloodstream infections caused by carbapenem-resistant Enterobacteriaceae: Results from the CARE study. Infectious Disease Week; October 4-8, 2017; San Francisco, CA. Poster 1853.
15. Golan Y, Cloutier DJ, Komirenko A, et al. Improved outcomes at late follow-up with plazomicin compared with meropenem in patients with complicated urinary tract infection, including acute pyelonephritis, in the EPIC study. Infectious Disease Week; October 4-8, 2017; San Diego, CA. Poster 1859.
16. Cloutier DJ, Miller LG, Komirenko A, et al. Evaluating once-daily plazomicin versus meropenem for the treatment of complicated urinary tract infection and acute pyelonephritis: Results from a phase 3 study (EPIC). American Society for Microbiology Microbe; June 1-5, 2017; New Orleans, LA. Oral presentation.
17. Ito-Horiyama T, Ishii Y, Ito A, et al. Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. *Antimicrob Agents Chemother*. 2016;60:4384–4386.
18. Ito A, Kohira N, Bouchillon SK, et al. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting gram-negative bacteria. *J Antimicrob Chemother*. 2016;71:670–677.
19. Kohira N, West J, Ito A, et al. In vitro antimicrobial activity of a siderophore cephalosporin, S-649266, against Enterobacteriaceae clinical isolates including carbapenem-resistant strains. *Antimicrob Agents Chemother*. 2016;60:729–734.
20. Tsuji M, Kazmierczak K, Hackel MM, et al. Cefiderocol (S-649266) susceptibility against globally isolated meropenem non-susceptible gram-negative bacteria containing serine and metallo-carbapenemase genes. Presented at American Society of Microbiology Meeting 2017, New Orleans, LA.
21. Portsmouth S, Van Veenhuyzen D, Echols R, et al. Clinical response of cefiderocol compared with imipenem/cilastatin in the treatment of adults with complicated urinary tract infections with or without pyelonephritis or acute uncomplicated pyelonephritis: Results from a multicenter, double-blind, randomized study (APEKS-cUTI) [abstract 1869]. In: Programs and Abstracts: Infectious Disease Week, San Diego; 2017.
22. Katsube T, Wajima T, Ishibashi T, et al. Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function. *Antimicrob Agents Chemother*. 2016;61:pii:e01381-16.
23. National Institutes of Health. A Multicenter, Randomized, Double-Blind, Parallel-Group, Clinical Study of S-649266 Compared With Meropenem for the Treatment of Hospital-Acquired Bacterial Pneumonia, Ventilator-Associated Bacterial Pneumonia, or Healthcare-Associated Bacterial Pneumonia Caused by Gram-Negative Pathogens. https://clinicaltrials.gov/ct2/show/NCT03032380. Accessed September 17, 2017.
24. A multicenter, randomized, open-label clinical study of S-649266 or best available therapy for the treatment of severe infections caused by carbapenem-resistant

gram-negative pathogens. https://clinicaltrials.gov/ct2/show/NCT02714595. Accessed September 17, 2017.

25. Castanheira M, Becker HK, Rhomberg PR, et al. Effect of β-lactamase inhibitor RPX7009 combined with meropenem tested against a large collection of KPC-producing Enterobacteriaceae. Presented at the Programs and Abstracts of the 54th Interscience Conference on Antimicrobials and Chemotherapy. Washington, DC. September 5-9, 2014. Abstr. C-777.
26. Livermore DM, Mushtaq S. Activity of biapenem (RPX2003) combined with the boronate β-lactamase inhibitor RPX7009 against carbapenem-resistant Enterobacteriaceae. *J Antimicrob Chemother*. 2013;68:1825–1831.
27. Goldstein EJC, Citron DM, Tyrrell KL, et al. In vitro activity of biapenem plus RPX7009, a carbapenem combined with a serine β-lactamase inhibitor, against anaerobic bacteria. *Antimicrob Agents Chemother*. 2013;56:2620–2630.
28. http://ir.themedicinescompany.com/phoenix.zhtml?c=122204&p=irol-newsArticle&id=1985873. Accessed May 1, 2015.
29. Wunderink R, Giamarellos-Bourboulis E, Rahav G, et al. Meropenem-vaborbactam vs. best available therapy for carbapenem-resistant Enterobacteriaceae infections in TANGO II: Primary outcomes by site of infection. Infectious Diseases Week; October 4-8, 2017; San Diego, CA. Poster 1867.
30. Paterson DL, Kwak EJ, Bhowmick T, et al. Meropenem-vaborbactam vs. best available therapy for carbapenem-resistant Enterobacteriaceae infections in TANGO II: Outcomes in immunocompromised patients. Infectious Diseases Week; October 4-8, 2017, San Diego, CA. Poster 1868.
31. Kahan FM, Kahan KS, Cassidy PJ, et al. The mechanism of action of fosfomycin (phosphonomycin). *Ann N Y Acad Sci*. 1974;335:364–386.
32. Michalopoulos AS, Lividitis IG, Gougoutas V. The revival of fosfomycin. *Int J Infect Dis*. 2011;15:e732–e739.
33. Kaye KS, Rice LB, Dane A, et al. Intravenous fosfomycin (ZTI-01) for the treatment of complicated urinary tract infections including acute pyelonephritis: Results from a multi-center, randomized, double-blind phase 2/3 study in hospitalized adults (ZEUS). Presented at Infectious Diseases Week; October 4-8, 2017, San Diego, CA.
34. Eckburg PB, Skarinsky D, Das A, et al. Phenotypic antibiotic resistance in ZEUS: A multi-center, randomized, double-blind phase 2/3 study of ZTI-01 versus piperacillin-tazobactam in the treatment of patients with complicated urinary tract infections including acute pyelonephritis. Presented at Infectious Diseases Week; October 4-8, 2017, San Diego, CA.
35. Flamm RK, Shortridge D, Rhomberg PR, et al. Fosfomycin activity when tested against gram-positive and gram-negative US isolates collected by the SENTRY antimicrobial surveillance program. Presented at American Society of Microbiology 2017, New Orleans, LA.
36. Poitier H, Tremeaux JC, Chavanet P, et al. Treatment of severe staphylococcal infections with cefotaxime and fosfomycin in combination. *J Antimicrob Chemother*. 1984;14(supplB):S277–S284.
37. Portier H, Kazmierczak A, Lucht F, et al. Cefotaxime in combination with other antibiotics for the treatment of severe methicillin-resistant staphylococcal infections. *Infection*. 1985;13(suppl 1):S123–S128.
38. Del Rio A, Gasch O, Moreno A, et al. Efficacy and safety of fosfomycin plus imipenem as rescue therapy for complicated bacteremia and endocarditis due to methicillin-resistant *Staphylococcus aureus*: a multicenter clinical trial. *Clin Infect Dis*. 2014;59:1105–1112.
39. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med*. 1991;115:674–680.
40. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653–665.
41. Falagas ME, Kanellopoulou MD, Karageorgopoulos DE, et al. Antimicrobial susceptibility of multi-drug resistant gram-negative bacteria to fosfomycin. *Eur J Clin Microbiol Infect Dis*. 2008;27:439–443.
42. Hong Nguyen H, Chen L, Hao B, et al. ZTI-01 activity against carbapenem-resistant and ceftazidime-avibactam resistant Enterobacteriaceae isolates with diverse resistance mechanism. Presented at American Society of Microbiology 2017, New Orleans, LA.
43. Drugeon HB, Courtieu AL. The role of culture media on the fosfomycin sensitivity of six *Serratia* strains and their resistant mutants. *Chemotherapy*. 1982;345–350.
44. Wenzler E, Ellis-Grosse E, Rodvold K. Pharmacokinetics, safety, and tolerability of single dose intravenous and oral fosfomycin in health volunteers. Presented at American Society of Microbiology 2017, New Orleans, LA.
45. Smith K, Tanaka SK, Appelbaum PC. Antistaphylococcal activity of MK-2764/PTK0796 compared to other agents. Presented at the Programs and Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, September 27-30, 2006;F1-1971.
46. Dubois J, Tanaka SK. In vitro activity of MK-2764/PTK0796 against *Legionella*. Presented at the Programs and Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, September 27-30, 2006;F1-1972.
47. Macone A, Donatelli J, Dumont T, et al. In vitro activity of PTK0796 against gram-positive and gram-negative organisms. Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, September 14-17, 2003.
48. Traczewski M, Brown S. PTK0796. In vitro potency and spectrum of activity compared to 10 other antimicrobial compounds. Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, September 14-17, 2003.
49. Flamm RK, Farrell DJ, Sader HS, et al. Antimicrobial activity of PTK 0796 (Omadacycline) and comparator agents against contemporary pathogens commonly associated with community-acquired respiratory tract infections collected during 2011 from the European Union. Proceedings of the 22nd European Congress of Clinical Microbiology and Infectious Diseases. London, March 30-April 3, 2012;P1449.
50. Waites KB, Crabb DM, Liu Y, et al. In vitro activities of omadacycline (PTK 0796) and other antimicrobial agents against human mycoplasmas and ureaplasmas. *Antimicrob Agents Chemother*. 2016;60:7431–7435.
51. Macone AB, Caruso BK, Leahy RG, et al. In vitro and in vivo antibacterial activities of omadacycline, a novel aminomethylcycline. *Antimicrob Agents Chemother*. 2014;58:1127–1135.
52. Gotfried MH, Rodvold KA, Horn K, et al. Pulmonary concentrations of the aminomethylcycline antibiotic omadacycline. American Thoracic Society; May 19-24, 2017; Washington, DC. Poster A3919.
53. Stets R, Popescu M, Gonong J, et al. A phase 3 randomized, double-blind, multi-center study to compare the safety and efficacy of IV to oral omadacycline to moxifloxacin for the treatment of adult subjects with CABP (OPTIC). Infectious Diseases Week; October 4-8, 2017; San Francisco, CA. Poster 1883.
54. O'Riordan WA, Green S, Overcash JS, et al. Efficacy of oral and iv omadacycline vs. linezolid for treating adult subjects with ABSSSI: Analysis by infection type and pathogen in the OASIS study. Presented at European Congress of Clinical Microbiology and Infectious Diseases. April 24, 2017; Vienna, Austria. Abstract 630.
55. Wilcox M, Cure-Bolt N, Chitra S, et al. Efficacy and safety of omadacycline in patients with acute bacterial skin and skin structure infections (ABSSSI) and high body mass index or diabetes: A subgroup analysis from the OASIS trial. Infectious Diseases Week; October 4-8, 2017; San Francisco, CA. Poster 1838.
56. Flamm RK, Rhomberg PR, Huband MD, et al. Activity of omadacycline tested against Enterobacteriaceae causing urinary tract infections from a global surveillance program (2014). Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17-21, 2015; San Diego, CA. Poster C-614.
57. Berg J, Tzanis E, Garrity-Ryan L, et al. Pharmacokinetics and safety of the aminomethylcycline antibiotic omadacycline in subjects with impaired renal function. American Society for Microbiology Microbe, June 1-5, 2017; New Orleans, LA. Poster 201.
58. Grossman TH, Starosta AL, Fyfe C, et al. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. *Antimicrob Agents Chemother*. 2012;56:2559–2564.
59. Horn PT, Sutcliffe JA, Walpole SM, et al. Pharmacokinetics, safety and tolerability of a novel fluorocycline (TP-434), following multiple oral dose administration with and without food. 49th Annual Meeting of the Infectious Disease Society of America. Boston, October 20-23, 2011. Abstr. 603.
60. Sutcliffe JA, Grossman T, Ronn M, et al. TP-434 has potential to treat complicated urinary tract infections (cUTI). Presented at the Programs and Abstracts of the 51st Interscience Conference on Antimicrobials and Chemotherapy. Chicago, September 17-20, 2011. Abstr. F1-1858.
61. Solomkin J, Evans D, Slepavicius A, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the investigating gram-negative infections treated with eravacycline (IGNITE 1) trial: a randomized clinical trial. *JAMA Surg*. 2017;152:224–232.
62. Sutcliffe JA, O'Brien W, Fyfe C, et al. Antimicrobial activity of eravacycline (TP-434), a novel fluorocycline against hospital and community pathogens. *Antimicrob Agents Chemother*. 2013;57:5548–5558.
63. Abdallah M, Olafisoye O, Cortes C, et al. Activity of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. *Antimicrob Agents Chemother*. 2015;59:1802–1805.
64. Connors KP, Housman ST, Pope JS, et al. Phase I, open-label, safety and pharmacokinetic study to assess bronchopulmonary disposition of intravenous eravacycline in healthy men and women. *Antimicrob Agents Chemother*. 2014;58:2113–2118.
65. Mendes RE, Farrell DJ, Flamm RK, et al. In vitro activity of lefamulin tested against *Streptococcus pneumoniae* with defined serotypes, including multidrug-resistant isolates causing lower respiratory tract infections in the United States. *Antimicrob Agents Chemother*. 2016;60:4407–4411.
66. Waites KB, Crabb DM, Duffy LB, et al. In vitro activities of lefamulin and other antimicrobial agents against macrolide-susceptible and macrolide-resistant *Mycoplasma pneumoniae* from the United States, Europe, and China. *Antimicrob Agents Chemother*. 2017;61:pii: e02008-16.
67. Zeitlinger M, Schwameis R, Burian A, et al. Simultaneous assessment of the pharmacokinetics of a pleuromutilin, lefamulin, in plasma, soft tissues and pulmonary epithelial lining fluid. *J Antimicrob Chemother*. 2016;71:1022–1026.
68. Prince WT, Izevic-Schoenfeld Z, Lell C. Phase II clinical study of BC-3781, a pleuromutilin antibiotic, in treatment of patients with acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother*. 2013;57:2087–2094.
69. National Institutes of Health. Study To Compare Lefamulin to Moxifloxacin (With or Without Linezolid) for the Treatment of Adults With Pneumonia (LEAP). https://clinicaltrials.gov/ct2/show/NCT02559310. Accessed December 14, 2017.
70. US Food and Drug Administration. Iclaprim for the Treatment of Complicated Akin and Skin-Structure Infections. https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4394b3-01-FDA.pdf. Accessed September 17, 2017.
71. US Food and Drug Administration. FDA Orphan Drugs and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=514415. Accessed September 17, 2017.
72. Huang D, Lodise T. Use of PK/PD systems analyses to determine the optimal fixed dosing regimen of iclaprim (ICL) for phase III ABSSSI clinical trial [abstract 1971]. In: Programs and Abstracts: Infectious Disease Week, New Orleans; 2017.
73. Huang DB, Hawser S, Gemmell CG, et al. In vitro activity of iclaprim against methicillin-resistant *Staphylococcus aureus* nonsusceptible to daptomycin, linezolid, or vancomycin: a pilot study. *Can J Infect Dis Med Microbiol*. 2017;2017:3948626.
74. Sader HS, Fritsche TR, Jones RN. Potency and bactericidal activity of iclaprim against recent clinical gram-positive isolates. *Antimicrob Agents Chemother*. 2009;53:2171–2175.
75. Huang DB, O'Riordan W, Overcash JS, et al. A phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin for the treatment of acute bacterial skin and skin structure infections suspected or confirmed to be due to gram-positive pathogens: REVIVE-1. *Clin Infect Dis*. 2018;66:1222–1229.
76. Huang DB, File TM Jr, Torres A, et al. A phase II randomized, double-blind, multicenter study to evaluate efficacy and safety of intravenous iclaprim versus vancomycin for the treatment of nosocomial pneumonia suspected or confirmed to be due to gram-positive pathogens. *Clin Ther*. 2017;39:1707–1718.
77. Andrews J, Honeybourne D, Ashby J, et al. Concentrations in plasma, epithelial lining fluid, alveolar macrophages and bronchial mucosa after a single intravenous dose of 1.6 mg/kg of iclaprim (AR-100) in healthy men. *J Antimicrob Chemother*. 2007;60:677–680.
78. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis*. 2008;197:1079–1081.
79. Dimasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003;22:151–185.
80. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? *Health Aff (Millwood)*. 2006;25:420–428.

37 Urinary Tract Agents: Nitrofurantoin, Fosfomycin, and Methenamine

James M. Horton

SHORT VIEW SUMMARY

Nitrofurantoin

- Nitrofurantoin is a first-line treatment for uncomplicated cystitis, with an efficacy of 88% to 92%. It is not indicated for pyelonephritis.
- The most common side effect is nausea, but the most serious is pulmonary hypersensitivity, which occurs in about 1 in 100,000 cases.
- Nitrofurantoin is a preferred treatment for cystitis during the last two trimesters of pregnancy but should be avoided at term or when delivery is imminent because of the risk of hemolytic anemia in the mother and baby.
- The American College of Obstetrics and Gynecology recommends that nitrofurantoin only be used in the first trimester if there are contraindications to safer antibiotics.

Fosfomycin

- Fosfomycin is administered orally as 3 g of powder mixed with at least one-half cup of water in a one-time dose before a meal.
- Fosfomycin is a first-line treatment for uncomplicated cystitis. A cure rate of 91% has been reported, but other data suggest fosfomycin is slightly less effective than other agents.
- Observational trials have shown that fosfomycin is effective against multidrug-resistant bacteria.

Methenamine

- Methenamine is hydrolyzed to formaldehyde in the acidic urine of the bladder. It is not effective in patients with indwelling Foley catheters or urostomies because of the rapid elimination of the drug from the bladder.
- Methenamine is indicated only for prevention of cystitis.

Nitrofurantoin and fosfomycin are considered first-line treatments for acute cystitis because of their pharmacologic properties.[1] At tolerated doses after oral administration, nitrofurantoin achieves adequate concentrations only in the urine.[2] Although parenteral fosfomycin has been used for systemic infections, the oral formulation is used only for urinary tract infections (UTIs). Methenamine becomes active only after chemical degradation in acidic bladder urine, to generate its active breakdown product, formaldehyde, and is used only for the prophylaxis of UTIs.[3]

NITROFURANTOIN

Nitrofurantoin is a member of a group of synthetic nitrofuran compounds and is a weak acid (pK_a 7.2) (Fig. 37.1).[4,5] A microcrystalline form was introduced in 1952, and macrocrystalline forms were developed in 1967. Mixtures of the microcrystalline and macrocrystalline forms are now available (Macrobid: 25 mg macrocrystals plus 75 mg monohydrate form), as are the macrocrystals alone (Macrodantin).[5]

Mechanisms of Drug Action and Bacterial Resistance

The mechanism of bactericidal activity appears to involve multiple sites, including inhibition of ribosomal translation, bacterial DNA damage, and interference with the Krebs cycle.[6–8] The role of each of these mechanisms is unclear.[7] It is metabolized by bacterial nitroreductases, which convert nitrofurantoin to a highly reactive electrophilic intermediate that attacks bacterial ribosomal proteins, causing complete inhibition of protein synthesis.[9]

Resistance to nitrofurantoin is uncommon, probably because of the multiple sites of action of the antibiotic.[1,2,10–12] A sixfold to sevenfold increase in resistance of *Escherichia coli* has been reported when the bacteria lack nitrofuran reductase enzyme activity.[10]

Spectrum of Activity

Nitrofurantoin is active against more than 90% of *E. coli* strains causing UTIs, but *Proteus* spp., *Serratia* spp., and *Pseudomonas* spp. have natural resistance.[6,8,12] In a study of catheter-associated UTIs, fewer than half of the *Klebsiella* spp., *Enterobacter* spp., and *Serratia* spp. are susceptible.[13] The drug has increasingly been used to treat enterococcal infections, including those due to vancomycin-resistant enterococci.[1,12] *Staphylococcus aureus* and *Staphylococcus saprophyticus* are usually susceptible.[1]

Most strains are considered susceptible to nitrofurantoin if the minimal inhibitory concentration (MIC) is 32 µg/mL or less.[14] Testing is indicated only for Enterobacteriaceae, *Staphylococcus* spp., and *Enterococcus* spp. *Pseudomonas aeruginosa* is almost universally resistant.[14]

Pharmacology

Absorption

Orally administered nitrofurantoin is 40% to 50% absorbed; absorption is improved when the drug is taken with food.[4,15] Absorption occurs principally in the small intestine. The microcrystalline form is more rapidly and completely absorbed than the macrocrystalline form (43% vs. 36%) but is associated with more gastrointestinal (GI) side effects.[4,15]

Distribution

Serum concentrations of nitrofurantoin are low or undetectable with standard oral doses.[12] Animal studies with intravenous nitrofurantoin suggest distribution in extracellular and intracellular tissues.[15] Drug concentration in the urine (50–250 µg/mL) easily exceeds the MIC of 32 µg/mL for susceptible organisms.[4] Concentrations in prostatic secretions are too low for effective use in prostate infections.[16] Concentrations in human breast milk are extremely low (0–0.5 µg/mL).[17,18] Biliary concentrations are about the same as those in the serum.[15]

Excretion

Nitrofurantoin is eliminated predominantly in the urine. Renal elimination involves glomerular filtration, tubular secretion, and tubular reabsorption.[15] Alkalinization of the urine can prevent the reabsorption of the nitrofurantoin in the renal tubules, but nitrofurantoin has reduced antimicrobial activity in alkaline urine.[2]

In patients with renal failure, nitrofurantoin excretion is proportionally decreased and should not be used in patients with substantial renal insufficiency.[5]

One study found that the treatment failure rate in elderly women with decreased renal function was the same for nitrofurantoin, ciprofloxacin, and trimethoprim-sulfamethoxazole (TMP-SMX).[19] The package insert recommends against using nitrofurantoin in patients with a creatinine

clearance less than 60 mL/min. The American Geriatrics Society recommends avoiding it if the clearance is less than 30 mL/min or for long-term suppression.[20] In patients with normal renal function, a small proportion of nitrofurantoin is eliminated by metabolism and biliary excretion, but these are minor pathways. No dose adjustment is needed in patients with liver failure.

Dosing

For therapy for UTIs, nitrofurantoin (Furadantin, Macrodantin) in the macrocrystalline formulation is given orally at 50 to 100 mg four times daily. For prophylaxis for recurrent UTIs, it is dosed at 50 to 100 mg once daily. The dose of the mixture of microcrystalline and macrocrystalline formulations (Macrobid) is 100 mg twice a day.

Indications

Nitrofurantoin is indicated only for the treatment and prophylaxis of lower UTIs.

Acute Uncomplicated Cystitis

Nitrofurantoin is now considered a first-line therapeutic agent for acute uncomplicated cystitis[1] because of the efficacy of a 5-day course of nitrofurantoin and the risks for collateral damage to the normal human microbes by fluoroquinolones (Table 37.1).[1]

Studies indicate a clinical cure rate with nitrofurantoin of 88% to 92% and a microbiologic cure rate of 81% to 92%.[1] Four randomized trials have demonstrated that nitrofurantoin has an efficacy equivalent to a 3-day course of TMP-SMX or ciprofloxacin. It is equivalent to one dose of fosfomycin. Past studies with 3 days of treatment with nitrofurantoin have demonstrated persistence of the pathogen in the periurethral, vaginal, and rectal areas,[21] so a 7-day course was recommended.[16] More recent studies have demonstrated the efficacy of a 5-day course of nitrofurantoin.[1] Overall, infections caused by *E. coli* respond well to nitrofurantoin,[2] but infections due to *Proteus* spp. and *Pseudomonas* spp. do not respond. Nitrofurantoin may have a role in treatment of nosocomial UTIs, but studies have been limited.[7]

Nitrofurantoin has been used safely in pregnant women[22] and in children.[4]

Acute Pyelonephritis and Complicated Urinary Tract Infections

Nitrofurantoin should not be used for treatment of pyelonephritis. It not only has failed to successfully treat pyelonephritis, but also two cases of bacteremia have been reported while patients were receiving nitrofurantoin therapy.[2]

Complicated UTIs resulting from anatomic abnormalities, indwelling Foley catheters, or nosocomial infections are more likely to be caused by organisms such as *Pseudomonas* that are resistant to nitrofurantoin. In men with recurrent bacteriuria, nitrofurantoin has reduced the recurrences by 40%, but other agents that achieve higher concentrations in the prostate are more effective.[23]

Many strains of vancomycin-resistant enterococci remain susceptible to nitrofurantoin, so it can be used for cystitis caused by these organisms.[24]

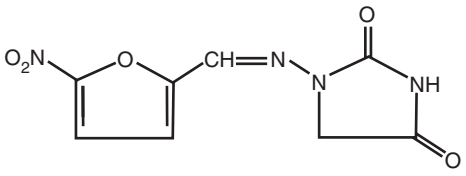

FIG. 37.1 **Chemical structure of nitrofurantoin.**

Prophylaxis for Recurrent Urinary Tract Infections

In young women with two or more episodes of symptomatic UTIs within 12 months, nitrofurantoin (100 mg) was effective and comparable to TMP-SMX in preventing further UTIs.[25,26] In a more heterogeneous population, nitrofurantoin was equivalent to cefaclor (250 mg at bedtime) or norfloxacin (200 mg at bedtime).[27,28] Nitrofurantoin was slightly less well tolerated owing to nausea.

For women in whom recurrence of infection is associated with sexual intercourse, a single dose of nitrofurantoin (100 mg) taken shortly after intercourse has been effective in preventing symptomatic infection.[28,29]

In postmenopausal women with recurrent UTIs, nitrofurantoin (100 mg every day) was more effective than an estriol-containing vaginal pessary in preventing symptomatic and asymptomatic bacteriuria.[30] In one pediatric study of children with intermittent catheterization, nitrofurantoin prevented *E. coli* UTIs, but infections due to resistant uropathogens increased.[25]

Antimicrobial prophylaxis is not of value in patients with long-term indwelling catheters.[22]

Adverse Effects

Pulmonary Reactions

Pulmonary reactions have been classified into acute and chronic forms.[4,31] Most studies cite a frequency of one or fewer cases per 100,000 courses of treatment,[17] although others have reported a rate of 1 in 5000 courses.[32–34] In 13,421 adults older than 65 years who were given short-course nitrofurantoin, there was no measurable increased risk of pulmonary complications; however, chronic administration was associated with pulmonary complications (risk ratio, 1.53).[35] Determining a precise incidence is difficult because the clinical presentation of nitrofurantoin lung disease overlaps with that of many other illnesses, such as pneumonia, exacerbation of bronchitis, heart failure, or chronic pulmonary fibrosis.[33,34]

Acute reactions occur within hours to weeks of drug exposure and are characterized by a reversible hypersensitivity phenomenon.[33,36] The reaction comprises the rapid onset of fever, cough, dyspnea, myalgia, and occasionally a rash. Peripheral blood eosinophilia (83% of cases), lower lobe infiltrates (94% of cases), and pleural effusions (20% of cases) often accompany these signs and symptoms. Sputum production, rash, pruritus, and chest discomfort may also occur. Lung biopsy can show vasculitis, alveolar exudates, and interstitial inflammation. Most

TABLE 37.1 Efficacy of Agents Commonly Used for Uncomplicated Urinary Tract Infections

ANTIBIOTIC	DOSE	CLINICAL EFFICACY (%, RANGE)	MICROBIOLOGIC EFFICACY (%, RANGE)	SIDE EFFECTS
Nitrofurantoin monohydrate/ macrocrystals	100 mg bid, 5–7 days	93 (84–95)	88 (86–92)	Nausea, headache, hepatic and pulmonary toxicity
Trimethoprim-sulfamethoxazole	160/800 mg bid, 3 days	93 (90–100)	94 (91–100)	Rash, hematologic toxicity, nausea
Fosfomycin	3-g single-dose packet	91	80 (78–83)	Diarrhea, headache
Fluoroquinolones	Dose varies, 3 days	90 (85–98)	91 (81–98)	Nausea, diarrhea, insomnia, prolonged QT interval
β-Lactam antibiotics	Dose varies, 3–5 days	89 (79–98)	82 (74–98)	Diarrhea, nausea, rash

Modified from Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update for the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. *2011;52:e103–e120.*

reports have occurred in women, which is consistent with the much greater use of nitrofurantoin in women than in men, and most cases occur in patients older than 40 years.[33,36] The reason for the frequency in older adults is unclear, but the American Geriatrics Society warns against the use of nitrofurantoin in patients older than 65 years with creatinine clearance of less than 30 mL/min or for prolonged courses.[20,37] Symptoms usually improve within 15 days with discontinuation of the drug, although case reports of fatalities have occurred.[31,36] One study cites the mortality from acute pulmonary reaction as 2 in 398 cases (0.5%).[36]

Chronic pulmonary reactions are 10 to 20 times less common, perhaps because the drug is infrequently used for prolonged therapy. These reactions occur after 1 to 6 months of therapy[31] and are characterized by nonproductive cough, dyspnea, interstitial infiltrates, and usually fever. Eosinophilia is less common than in patients with acute reactions. Abnormal results of liver enzyme studies (40%) and positive assays for antinuclear antibodies have been reported. Improvement can occur with discontinuation of the drug, but about half of the affected persons have persistent mild signs of pulmonary fibrosis.[31] An interstitial pattern on chest tomography has been reported but does not correlate with progression of disease.[38] The mortality rate from the chronic pulmonary reaction is reported as 4 in 49 cases (8%).[36]

The most important treatment includes early recognition of the complication and prompt discontinuation of the drug. The chronic pulmonary complications can be insidious, leading to erroneous diagnoses, such as congestive heart failure.[33] Corticosteroids have been used in some patients who recovered, but no large trials exist.[39] Bronchiolitis obliterans and organizing pneumonia have been reported.[40] Desquamative interstitial pneumonitis has been reported in a child.[41] Exacerbation of hereditary angioedema with lip and throat swelling has been described.[42]

Gastrointestinal Reactions

The tolerability of nitrofurantoin is limited by the GI adverse effects, which occur particularly with the microcrystalline formulation.[18] The macrocrystalline formulations are associated with nausea and vomiting in 17% of patients, compared with 39% in patients using the microcrystalline forms at doses of 100 mg four times daily. Slower dissolution of the macrocrystalline formulation is believed to be responsible for its lower frequency of GI side effects. In a double-blind study, ciprofloxacin had fewer episodes of nausea than did nitrofurantoin (3% vs. 11%).[43]

Cutaneous Reactions

Rashes occur in about 1% of patients being treated with nitrofurantoin. TMP-SMX is significantly more likely to cause a rash than nitrofurantoin (4% vs. 0.4%).[43] Most cutaneous reactions with nitrofurantoin are relatively mild, particularly when compared with those that may occur after therapy with TMP-SMX.[18] Cutaneous reactions have included Sweet syndrome, antineutrophilic cytoplasmic antibody-associated vasculitis, and lupus.[44]

Hepatic Reactions

Hepatic reactions occur at about the same frequency as the pulmonary reactions and can occur at the same time.[36] Acute hepatitis associated with short-term use of nitrofurantoin was self-limited and reversible in 8 patients in one study.[45] Prolonged use of nitrofurantoin has been associated with chronic active hepatitis, cirrhosis, and death.[46] In one study of 42 patients with nitrofurantoin-induced hepatitis, two patients (5%) died and 18% developed chronic hepatitis.[47] In these cases antinuclear antibodies are often present, but eosinophilia occurs less frequently.[46]

Hematologic Reactions

Hemolytic anemia in patients receiving nitrofurantoin is most commonly associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[48] Hemolysis from deficiencies in enolase and glutathione peroxidases has been described, as have folic acid–responsive anemias.[49] Eosinophilia has been described in patients with pulmonary and hepatic reactions. Other leukocyte dyscrasias are uncommonly reported.[36]

Peripheral Neuropathy

A peripheral sensorimotor neuropathy has been reported uncommonly but is especially noted in patients with renal failure who are receiving the drug.[18,36] The neuropathy is characterized by distal dysesthesias and paresthesias. Distal muscle weakness also can occur.[49] Histopathology shows demyelination and axonal degeneration. Resolution of symptoms is slow and variable after cessation of the drug.

Systemic Inflammatory Response Syndrome

One case of systemic inflammatory response syndrome has been described in a patient on long-term prophylactic therapy with nitrofurantoin. The syndrome resolved with discontinuation of the drug.[50]

Drug Interactions

There has been one case report of fluconazole precipitating nitrofurantoin pulmonary toxicity.[51] Theoretically, nitrofurantoin can precipitate methemoglobinemia; other drugs causing methemoglobinemia, most commonly dapsone or benzocaine, in high-risk patients should be avoided.[52] Nitrofurantoin can inhibit the oral live typhoid or cholera vaccines.[5] Magnesium-containing compounds can inhibit its absorption.[5] It also interacts with probenecid. Nitrofurantoin has been associated with hyperkalemia; thus drugs such as spironolactone and triamterene should be avoided.[53]

Use in Children and During Pregnancy

Adverse events in children appear to be similar to those in adults. Nitrofurantoin is not recommended for neonates.[54] Studies on safety of nitrofurantoin during pregnancy have mixed results. It is the most commonly prescribed medication during pregnancy and is considered a pregnancy category B drug.[55,56] Although the drug crosses the placenta, only low concentrations reach the amniotic fluid.[57] When adverse events in 165 pregnant patients receiving nitrofurantoin were reviewed, no increased incidence was found of fetal loss or fetal abnormality when compared with the general population.[58] Other studies have confirmed these findings.[49,59,60] Although nitrofurantoin is mutagenic in bacterial studies, no teratogenicity or carcinogenicity has been found in animal studies.[18] A meta-analysis of 91,115 exposed cases and 1,578,745 unexposed controls in the first trimester showed no increased risk on nitrofurantoin during pregnancy in cohort studies, but meta-analysis of the three case-control studies did show some increased risk.[61] In a retrospective study, the risk of cleft lip or palate in babies born to mothers who received nitrofurantoin periconceptionally was increased compared with penicillin (odds ratio, 1.97), but the absolute risks remained low compared with the risk of UTIs.[62] The American College of Obstetricians and Gynecologists recommends avoiding nitrofurantoin in the first trimester unless there are no safer alternatives.[63] Case reports of hemolytic anemia in pregnant women with G6PD deficiency exist; the complication can be confused with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets).[64] Nitrofurantoin should be avoided at term, if labor is imminent, or in neonates because of concerns for hemolytic anemia and jaundice in the baby.[18]

It is excreted in small amounts in the breast milk; theoretically neonates exposed to nitrofurantoin from breast milk could develop hemolytic anemia, although no cases have been reported.[65]

FOSFOMYCIN

Fosfomycin was discovered in 1969 as a member of a novel class of phosphonic antibiotics (Fig. 37.2). It has been used as a parenteral antibiotic for systemic infections but more recently has been available

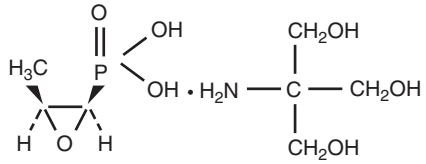

FIG. 37.2 Chemical structure of fosfomycin.

as an oral formulation that is used solely for treatment of uncomplicated cystitis.[66]

Mechanism of Action and Antimicrobial Activity

Fosfomycin blocks cell wall synthesis by inhibiting the synthesis of peptidoglycans. The drug requires transport into the cell wall by two main transport systems: the L-α-glycerophosphate and the hexose phosphate uptake systems.[66] G6PD must be added to the medium to determine the in vitro susceptibilities. Fosfomycin has been available in Europe for parenteral use, but in the United States it is available only in the oral form for treatment of UTIs.[66]

Fosfomycin has broad-spectrum bactericidal activity against staphylococci, enterococci, *Haemophilus* spp., and most enteric gram-negative bacteria. It also has excellent activity against most *E. coli,* including 95.5% of extended-spectrum β-lactamase (ESBL)-producing *E. coli.*[66] ESBL 025b/B2 *E. coli* strains are resistant to fosfomycin.[66] *Klebsiella* spp., *Enterobacter* spp., and *Serratia* spp. have higher MICs; fosfomycin has activity against only 57.6% of ESBL-producing *Klebsiella* spp.[67] *P. aeruginosa* is variably susceptible to fosfomycin, with MICs ranging from 4 to more than 512 μg/mL.[66] *Acinetobacter baumannii* is usually resistant. Fosfomycin retains excellent in vitro activity against both *Enterococcus faecalis* (97.7%) and *Enterococcus faecium* (100%).[68] Susceptibilities to fosfomycin should be determined by disk diffusion and not broth dilution.[14]

Most resistance is chromosomally mediated and interferes with the transport of the antibiotic into the bacteria.[69] Three resistance genes carried by plasmids—*fosA* in *P. aeruginosa, fosB* in *S. aureus,* and *fosX* in *Listeria monocytogenes*—confer resistance by breaking the oxirane ring of the fosfomycin molecule.[70]

Pharmacology

Fosfomycin is best absorbed if given before food intake, with up to 58% absorbed and excreted in the urine.[66] The fosfomycin molecule (138 Da) is smaller than other antibiotics, and it diffuses across membranes easily. It is water soluble and hydrolyzed to an active form but not metabolized. After a 3-g oral dose, the peak serum levels are 22 to 32 μg/mL at 4 hours. Fosfomycin achieves high concentrations in the urine of 2000 μg/mL and maintains high levels for more than 24 hours.[69] Its long half-life allows for one dose to treat uncomplicated cystitis.

Dosing

Fosfomycin (Monurol) is administered as a powder containing 3 g of the drug mixed into a slurry with at least one-half cup (4 oz) of water before meals. It should never be taken as the dry powder formulation.[71] It is generally administered as one dose for acute uncomplicated cystitis, but the dose has been repeated every 3 days to successfully treat more complicated UTIs.[71]

Indications

Acute Uncomplicated Cystitis

The clinical efficacy of one (3 g) dose of fosfomycin (91% cure) is comparable to nitrofurantoin (93%), TMP-SMX (93%), and fluoroquinolones (90%) in acute uncomplicated cystitis.[1] The microbiologic cure rate of fosfomycin (80%) is lower than comparable antibiotics at 88% to 94%.[1] One review reports unpublished data that show fosfomycin is slightly less effective than these comparable agents.[1] The Infectious Diseases Society of America lists fosfomycin as first-line therapy for cystitis because of the ease of administration but cautions that it might be slightly less effective than other agents.[1] One meta-analysis demonstrated equivalent clinical success between fosfomycin and other antibiotics for UTIs.[72]

One niche use for fosfomycin is in the treatment of multidrug-resistant organisms. There has been increasing use against ESBL- and *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae.[73] Observational trials indicate that fosfomycin can be effective in treatment of UTIs due to multidrug-resistant organisms such as KPC-producing Enterobacteriaceae with 3-g doses repeated every 48 to 72 hours.[73,74] One study documented a parallel increase in resistance to fosfomycin among ESBL-producing *E. coli* with more frequent use of fosfomycin in the community.[75]

Fosfomycin is not indicated for pyelonephritis.[1] Shrestha and Tomford[69] report one case of the successful treatment of prostatitis with 3 g fosfomycin given orally every 3 days for 3 weeks. It has been used for prophylaxis of transrectal ultrasound-guided prostate biopsy.[76]

Adverse Effects

Fosfomycin has been associated with diarrhea, vaginitis, nausea, and headache at rates comparable to those of other antibiotics used for UTIs.[66,71] Cases of optic neuritis and hearing loss have been reported.[66,71] At least one case of anaphylaxis due to fosfomycin has been reported,[77] as well as a single case of *Clostridioides difficile* (formerly *Clostridium difficile*) diarrhea.[66]

Use During Pregnancy

Fosfomycin is approved for use during pregnancy and is considered a US Food and Drug Administration (FDA) category B drug; it is one of the choices for treatment of cystitis during pregnancy.[71,78] Safety with breast-feeding and in children younger than 12 years has not been established.

METHENAMINE

The chemical structure of methenamine (hexamethylenetetramine) is shown in Fig. 37.3. It is available as a salt of mandelic acid (Mandelamine) or hippuric acid (benzoyl amino acetic acid) (Hiprex) or without these acids (Urised, Prosed/DS, Urimax).[79]

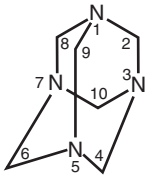

FIG. 37.3 Chemical structure of methenamine.

Mechanism of Action and Antimicrobial Activity

Methenamine itself has little antibacterial activity, but at acid pH each molecule of methenamine is hydrolyzed to produce four molecules of ammonia and six molecules of formaldehyde.[80,81]

The active product in formaldehyde is a nonspecific denaturant of proteins and nucleic acids with broad-spectrum antimicrobial activity. Microbial resistance has not been described, but *Proteus* spp. may produce urease, causing an alkaline urine and preventing the conversion of methenamine to formaldehyde.

Pharmacology

Absorption and Distribution

Methenamine is rapidly absorbed after oral administration, and 82% to 88% is recovered in the urine of normal volunteers in the 24 hours after a 1-g dose.[82] Methenamine may be partially degraded in the presence of gastric acid before absorption.[83] An enteric-coated formulation prevents this degradation but slows absorption. Methenamine is widely distributed to tissues and crosses the placenta, and concentrations in breast milk are similar to those in the plasma.[84] The drug is 95% excreted through the kidneys by glomerular filtration and tubular secretion.[82] The elimination half-life from the serum is 3 to 4 hours. The amount of accumulation of methenamine in patients with renal failure is not known.[85]

Factors Affecting Formaldehyde Concentrations in Urine

Antimicrobial activity correlates with urinary formaldehyde concentrations; those concentrations are determined by (1) the methenamine concentrations in the urine, (2) the rate of hydrolysis of methenamine to formaldehyde, and (3) the rate of urine loss from the bladder by voiding or drainage. Methenamine concentrations usually reach 150 μg/L but are lower with higher volumes of urine. The conversion to formaldehyde

increases with more acidic urine; at a urine pH of 6.8 or greater no hydrolysis occurs. The time required for effective concentrations of formaldehyde is 6 hours at a pH of 6.5 and 2 hours at a pH of 5.6.[86,87] A formaldehyde concentration of 25 µg/mL requires 2 hours of bacterial exposure to be effective. Methenamine is ineffective in the presence of indwelling bladder catheters or frequent catheterization because the rapid elimination of urine does not allow time for the conversion into formaldehyde. It is also ineffective for treatment of upper UTIs.

Acidification of Urine During Methenamine Treatment

A urine pH less than 6 is required for antibacterial activity of methenamine. Ascorbic acid has been given to aid urine acidification.[80]

Dosing

For adults and children older than 12 years, methenamine hippurate is usually given at a dose of 1 g orally twice daily. For children between 6 and 12 years, the dose is 500 mg to 1 g twice daily.[79]

Indications

Methenamine should not be used for treatment of established UTIs and is not effective for pyelonephritis.

Methenamine is effective in preventing recurrent lower UTIs. In young, otherwise healthy women, 1 g of methenamine twice daily reduced the frequency of recurrent cystitis by 73%.[88] Methenamine mandelate (500 mg four times daily) with ascorbic acid reduced cystitis by 56%.[89] This drug is not as effective in suppressing UTIs when compared with TMP-SMX or nitrofurantoin.[90]

Methenamine is not effective in preventing UTIs in patients with indwelling bladder catheters.[91] Trials of methenamine in patients undergoing intermittent catheterization have had variable results.[91,92] In patients undergoing bladder retraining with catheterization, voiding and controlled drinking resulted in a decrease in urinary tract infection over 21 days.[92] More prolonged use may only postpone the bacteriuria.

Adverse Effects

Side effects from methenamine are infrequent and usually mild.[80,89] Nausea, vomiting, rashes, or pruritus have been described.[80] At higher doses, GI intolerance and hemorrhagic cystitis may occur, possibly related to the high bladder concentration of formaldehyde.[93] Methenamine may predispose to the development of urate crystals in the urine and may cause precipitation of sulfonamides. Because of the ammonia produced by the hydrolysis of methenamine, use of this drug should be avoided in patients with liver failure. The safety of methenamine in renal failure has not been established.[94] The data about use in pregnancy are limited; the FDA categorizes methenamine as pregnancy risk C.[95]

Key References

The complete reference list is available online at Expert Consult.

1. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update for the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:e103–e120.
3. Gleckman R, Alvarez S, Joubert DW, et al. Drug therapy reviews: methenamine mandelate and methenamine hippurate. *Am J Hosp Pharm*. 1979;36:1509–1512.
4. Gleckman R, Alvarez S, Joubert DW. Drug therapy reviews: nitrofurantoin. *Am J Hosp Pharm*. 1979;36:342–351.
5. UpToDate: Nitrofurantoin drug information. 2013. http://www.uptodate.com/contents/nitrofurantoin-drug-information. Accessed March 2013.
6. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. *Drugs*. 2001;61:353–364.
9. McOsker CC, Fitzpatrick PM. Nitrofurantoin: mechanism of action and implications for resistance development in common uropathogens. *J Antimicrob Chemother*. 1994;33:23–30.
10. McCalla D, Reuvers A, Kaiser C. Mode of action of nitrofurazone. *J Bacteriol*. 1970;104:1126–1134.
13. Wazait HD, Patel HR, Veer V, et al. Catheter-associated urinary tract infections: prevalence of uropathogens and pattern of antimicrobial resistance in a UK hospital (1996-2001). *BJU Int*. 2003;91:806–809.
14. *Performance Standards for Antimicrobial Susceptibility;* Twenty-Third Informational Supplement. CLSI document M100-MS23. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
15. Conklin J. The pharmacokinetics of nitrofurantoin and its related bioavailability. *Antibiot Chemother*. 1978;25:233–252.
18. D'Arcy P. Nitrofurantoin. *Drug Intell Clin Pharm*. 1985;19:540–547.
21. Hooton TM, Winter C, Tiu F, et al. Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. *JAMA*. 1995;273:41–45.
22. Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med*. 1993;239:1328–1334.
24. Zhanel GG, Hoban DJ, Karlowsky JA. Nitrofurantoin is active against vancomycin-resistant enterococci. *Antimicrob Agents Chemother*. 2001;45:324–326.
25. Schlager TA, Anderson SM, Trudell JM. Nitrofurantoin prophylaxis for bacteriuria and urinary tract infection in children with neurogenic bladder on intermittent catheterization. *J Pediatr*. 1998;132:704–708.
26. Stamm WE, Counts GW, Wagner KF, et al. Antimicrobial prophylaxis of recurrent urinary tract infections. *Ann Intern Med*. 1980;92:770–775.
27. Brumfitt W, Hamilton-Miller J. Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. *J Antimicrob Chemother*. 1998;42:363–371.
29. Pfau A, Sacks TG. Effective prophylaxis for recurrent urinary tract infection during pregnancy. *Clin Infect Dis*. 1992;14:810–814.
30. Raz R, Colodner R, Rohanna Y, et al. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. *Clin Infect Dis*. 2003;36:1362–1368.
31. Sovijärvi A, Lemola M, Stenius B, et al. Nitrofurantoin-induced acute, subacute and chronic pulmonary reactions. *Scand J Respir Dis*. 1977;58:41–50.
36. Holmberg L, Boman G. Pulmonary reactions to nitrofurantoin. *Eur J Respir Dis*. 1981;62:180–189.
38. Sheehan RE, Wells AU, Milne DM. Nitrofurantoin-induced lung disease: two cases demonstrating resolution of apparently irreversible CT abnormalities. *J Comput Assist Tomogr*. 2000;24:259–261.
39. Hardak E, Berger G, Krivoy N, et al. Nitrofurantoin pulmonary toxicity: neglected threat. *Curr Drug Saf*. 2010;5:125–128.
43. Iravani A, Klimberg I, Briefer C, et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother*. 1999;43:67–75.
45. Goldstein LI, Ishak KG, Burns WM. Hepatic injury associated with nitrofurantoin therapy. *Dig Dis*. 1974;19:987–998.
46. Sharp JR, Ishak KG, Zimmerman H. Chronic active hepatitis and severe hepatic necrosis associated with nitrofurantoin. *Ann Intern Med*. 1980;92:14–19.
50. Forster CJ, Cohee BM, Wood-Morris RN, et al. Nitrofurantoin-induced systemic inflammatory response syndrome. *Am J Med Sci*. 2009;338:338–340.
51. Linnebar SA, Parnes BL. Pulmonary and hepatic toxicity due to fluconazole and nitrofurantoin treatment. *Ann Pharmacother*. 2004;38:612–616.
54. Coraggio MJ, Gross TP, Roscelli JD. Nitrofurantoin toxicity in children. *Pediatr Infect Dis J*. 1989;8:163–166.
58. Hailey F, Fort H, Williams J, et al. Foetal safety of nitrofurantoin macrocrystals therapy during pregnancy: a retrospective analysis. *J Int Med Res*. 1983;11:364–369.
59. Kass EH. Bacteriuria and pyelonephritis of pregnancy. *Arch Intern Med*. 1960;105:194–198.
60. Czeizel AE, Rockenbauer M, Sorensen HT, et al. Nitrofurantoin and congenital abnormalities. *Eur J Obstet Gynecol Reprod Biol*. 2001;95:119–126.
61. Goldberg O, Moretti M, Levy A, et al. Exposure to nitrofurantoin during early pregnancy and congenital malformations: a systematic review and meta-analysis. *J Obstet Gynaecol Can*. 2015;37:150–156.
63. ACOG Committee Opinion No. 404. Sulfonamides, nitrofurantoin and risk of birth defects. *Obstet Gynecol*. 2011;117:1484–1485.
66. Raz R. Fosfomycin: an old–new antibiotic. *Clin Microbiol Infect*. 2012;18:4–7.
67. Liu HY, Lin HC, Lin YC, et al. Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan. *J Microbiol Immunol Infect*. 2011;44:364–368.
68. Butcu M, Akcay SS, Inan AS, et al. In vitro susceptibility of enterococci strains isolated from urine samples to fosfomycin and other antibiotics. *J Infect Chemother*. 2011;17:575–578.
69. Shrestha NK, Tomford JW. Fosfomycin: a review. *Infect Dis Clin Pract*. 2001;10:255–260.
73. Pullukcu H, Tasbakan M, Sipahi OR, et al. Fosfomycin in the treatment of extended spectrum beta-lactamase–producing *Escherichia coli*–related lower urinary tract infections. *Int J Antimicrob Agents*. 2007;29:62–65.
74. Rodriguez-Bano J, Alcala JC, Cisneros JM, et al. Community infections caused by extended-spectrum beta-lactamase–producing *Escherichia coli*. *Arch Intern Med*. 2008;168:1897–1902.
75. Oteo J, Bautista V, Lara N, et al. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. *J Antimicrob Chemother*. 2010;65:2459–2463.
77. Rosales MJ, Vega F. Anaphylactic shock due to fosfomycin. *Allergy*. 1998;53:905–906.
78. Reeves DS. Treatment of bacteriuria in pregnancy with single dose fosfomycin trometamol: a review. *Infection*. 1992;20(suppl 4):S313–S316.
80. Gleckman R, Alvarez S, Joubert DW, et al. Drug therapy reviews: methenamine mandelate and methenamine hippurate. *Am J Hosp Pharm*. 1979;36:1509–1512.
82. Klinge E, Männistö P, Mäntylä R, et al. Pharmacokinetics of methenamine in healthy volunteers. *J Antimicrob Chemother*. 1982;9:209–216.
86. Musher DM, Griffith DP. Generation of formaldehyde from methenamine: effect of pH and concentration, and antibacterial effect. *Antimicrob Agents Chemother*. 1974;6:708–711.
88. Cronberg S, Welin C-O, Henriksson L, et al. Prevention of recurrent acute cystitis by methenamine hippurate: double blind controlled crossover long term study. *Br Med J (Clin Res Ed)*. 1987;294:1507–1508.
90. Brumfitt W, Cooper J, Hamilton-Miller J. Prevention of recurrent urinary infections in women: a comparative trial between nitrofurantoin and methenamine hippurate. *J Urol*. 1981;126:71–74.
92. Kevorkian CG, Merritt JL, Llstrup DM. Methenamine mandelate with acidification: an effective urinary antiseptic in patients with neurogenic bladder. *Mayo Clin Proc*. 1984;59:523–529.
93. Ross RR, Conway GF. Hemorrhagic cystitis following accidental overdose of methenamine mandelate. *Am J Dis Child*. 1970;119:86–87.

References

1. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update for the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:e103–e120.
2. Richards WA, Riss EM, Kass EH, et al. Nitrofurantoin. *Arch Intern Med*. 1955;96:437–450.
3. Gleckman R, Alvarez S, Joubert DW, et al. Drug therapy reviews: methenamine mandelate and methenamine hippurate. *Am J Hosp Pharm*. 1979;36:1509–1512.
4. Gleckman R, Alvarez S, Joubert DW. Drug therapy reviews: nitrofurantoin. *Am J Hosp Pharm*. 1979;36:342–351.
5. UpToDate: Nitrofurantoin drug information. 2013. http://www.uptodate.com/contents/nitrofurantoin-drug-information. Accessed March 2013.
6. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. *Drugs*. 2001;61:353–364.
7. McKinnell JA, Stollenwerk NS, Jung CW, et al. Nitrofurantoin compares favorably to recommended agents as empirical treatment of uncomplicated urinary tract infections in a decision and cost analysis. *Mayo Clin Proc*. 2011;86:480–488.
8. Cunha BA, Shoch PE, Hage JR. Nitrofurantoin: preferred empiric therapy for community-acquired lower urinary tract infections. *Mayo Clin Proc*. 2011;86:1243–1248.
9. McOsker CC, Fitzpatrick PM. Nitrofurantoin: mechanism of action and implications for resistance development in common uropathogens. *J Antimicrob Chemother*. 1994;33:23–30.
10. McCalla D, Reuvers A, Kaiser C. Mode of action of nitrofurazone. *J Bacteriol*. 1970;104:1126–1134.
11. McOsker CC, Fitzpatrick PM. Nitrofurantoin: mechanism of action and implications for resistance development in common uropathogens. *J Antimicrob Chemother*. 1994;33:23–30.
12. Cunha BA. New uses for older antibiotics: nitrofurantoin, amikacin, colistin, polymyxin B, doxycycline, and minocycline revised. *Med Clin North Am*. 2006;90:1089–1107.
13. Wazait HD, Patel HR, Veer V, et al. Catheter-associated urinary tract infections: prevalence of uropathogens and pattern of antimicrobial resistance in a UK hospital (1996-2001). *BJU Int*. 2003;91:806–809.
14. *Performance Standards for Antimicrobial Susceptibility*; Twenty-Third Informational Supplement. CLSI document M100-MS23. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
15. Conklin J. The pharmacokinetics of nitrofurantoin and its related bioavailability. *Antibiot Chemother*. 1978;25:233–252.
16. Dunn BL, Stamey TA. Antibacterial concentrations in prostatic fluid, 1. Nitrofurantoin. *J Urol*. 1967;97:505–507.
17. Varsano IM, Fischl JM, Tikvah P, et al. The excretion of orally ingested nitrofurantoin in human milk. *J Pediatr*. 1973;82:886–887.
18. D'Arcy P. Nitrofurantoin. *Drug Intell Clin Pharm*. 1985;19:540–547.
19. Singh N, Gandhi S, McArthur E, et al. Kidney function and the use of nitrofurantoin to treat urinary tract infections in older women. *CMAJ*. 2015;187:648–856.
20. American Geriatrics Society. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. Potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63:2227–2246.
21. Hooton TM, Winter C, Tiu F, et al. Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. *JAMA*. 1995;273:41–45.
22. Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med*. 1993;239:1328–1334.
23. Freeman RB, Smith WM, Richardson JA, et al. Long-term therapy for chronic bacteriuria in men. *Ann Intern Med*. 1975;83:133–147.
24. Zhanel GG, Hoban DJ, Karlowsky JA. Nitrofurantoin is active against vancomycin-resistant enterococci. *Antimicrob Agents Chemother*. 2001;45:324–326.
25. Schlager TA, Anderson SM, Trudell JM. Nitrofurantoin prophylaxis for bacteriuria and urinary tract infection in children with neurogenic bladder on intermittent catheterization. *J Pediatr*. 1998;132:704–708.
26. Stamm WE, Counts GW, Wagner KF, et al. Antimicrobial prophylaxis of recurrent urinary tract infections. *Ann Intern Med*. 1980;92:770–775.
27. Brumfitt W, Hamilton-Miller J. Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. *J Antimicrob Chemother*. 1998;42:363–371.
28. Vosti KL. Recurrent urinary tract infections. *JAMA*. 1975;231:934–940.
29. Pfau A, Sacks TG. Effective prophylaxis for recurrent urinary tract infection during pregnancy. *Clin Infect Dis*. 1992;14:810–814.
30. Raz R, Colodner R, Rohanna Y, et al. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. *Clin Infect Dis*. 2003;36:1362–1368.
31. Sovijärvi A, Lemola M, Stenius B, et al. Nitrofurantoin-induced acute, subacute and chronic pulmonary reactions. *Scand J Respir Dis*. 1977;58:41–50.
32. Krause M, Ruef C. Miscellaneous antibacterial drugs. In: Dukes MNG, Aronson JK, eds. *Meyler's Side Effects of Drugs*. 14th ed. Amsterdam: Elsevier BV; 2000:884–885.
33. Tatley M. Pulmonary reactions to nitrofurantoin. *Medsafe N Z*. 2002;23:24–25. Updated June 10, 2013.
34. Jick SS, Jick H, Walker AM, et al. Hospitalizations for pulmonary reactions following nitrofurantoin use. *Chest*. 1989;96:512–515.
35. Santos JM, Batech M, Pelter MA, et al. Evaluation of the risk of nitrofurantoin lung injury and its efficacy in diminished kidney function in older adults in a large integrated healthcare system. *J Am Geriatr Soc*. 2016;64:798–805.
36. Holmberg L, Boman G. Pulmonary reactions to nitrofurantoin. *Eur J Respir Dis*. 1981;62:180–189.
37. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60:616–631.
38. Sheehan RE, Wells AU, Milne DM. Nitrofurantoin-induced lung disease: two cases demonstrating resolution of apparently irreversible CT abnormalities. *J Comput Assist Tomogr*. 2000;24:259–261.
39. Hardak E, Berger G, Krivoy N, et al. Nitrofurantoin pulmonary toxicity: neglected threat. *Curr Drug Saf*. 2010;5:125–128.
40. Robinson C, Nyi PP. Probable nitrofurantoin-induced bronchiolitis obliterans with organizing pneumonia. *Am J Health Syst Pharm*. 2009;66:1919–1922.
41. Hage P, El Haije M. Nitrofurantoin-induced desquamative interstitial pneumonitis in a 7-year old child. *Pediatr Infect Dis J*. 2011;30:363.
42. Eastman J, Zuraw B. Angioedema due to allergy in a patient with hereditary angioedema: all that glitters is not gold. *Ann Allergy Asthma Immunol*. 2016;116:366–379.
43. Iravani A, Klimberg I, Briefer C, et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother*. 1999;43:67–75.
44. Kwok T, Mahmood MN, Salopek TG. Sweet syndrome with panniculitis, arthralgia, episcleritis and neurologic involvement precipitated by antibiotics. *Dermatol Online J*. 2014;20:1.
45. Goldstein LI, Ishak KG, Burns WM. Hepatic injury associated with nitrofurantoin therapy. *Dig Dis*. 1974;19:987–998.
46. Sharp JR, Ishak KG, Zimmerman H. Chronic active hepatitis and severe hepatic necrosis associated with nitrofurantoin. *Ann Intern Med*. 1980;92:14–19.
47. de Boer YS, Kosinski AS, Urban TJ, et al. Features of autoimmune hepatitis in patients with drug-induced liver injury. *Clin Gastroenterol Hepatol*. 2017;15:103–112.
48. Gait J. Hemolytic reactions to nitrofurantoin in patients. *Ann Pharmacother*. 1990;24:1210–1213.
49. Shah R, Wade G. Reappraisal of the risk/benefit of nitrofurantoin. *Adverse Drug React Acute Poisoning Rev*. 1989;8:183–201.
50. Forster CJ, Cohee BM, Wood-Morris RN, et al. Nitrofurantoin-induced systemic inflammatory response syndrome. *Am J Med Sci*. 2009;338:338–340.
51. Linnebar SA, Parnes BL. Pulmonary and hepatic toxicity due to fluconazole and nitrofurantoin treatment. *Ann Pharmacother*. 2004;38:612–616.
52. Busker RW, van Henegouwen GM, Menek RF, et al. Formation of methemoglobin by photoactivation of nitrofurantoin or of 5-nitrofurfural in rats exposed to UV-a light. *Toxicology*. 1988;51:255–266.
53. Antoniou T, Gomes T, Mamdani MM, et al. Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: nested case-control study. *BMJ*. 2011;343:d5228.
54. Coraggio MJ, Gross TP, Roscelli JD. Nitrofurantoin toxicity in children. *Pediatr Infect Dis J*. 1989;8:163–166.
55. Palmsten K, Hernandez-Diaz S, Chambers CD, et al. The most commonly dispensed prescription medications among pregnant women enrolled in the United States medicaid program. *Obstet Gynecol*. 2015;126:465–473.
56. Bookstave PB, Bland CM, Griddin B, et al. A review of antibiotic use in pregnancy. *Pharmacotherapy*. 2015;35:1052–1062.
57. Perry J, Leblanc A. Transfer of nitrofurantoin across the human placenta. *Tex Rep Biol Med*. 1967;25:265–269.
58. Hailey F, Fort H, Williams J, et al. Foetal safety of nitrofurantoin macrocrystals therapy during pregnancy: a retrospective analysis. *J Int Med Res*. 1983;11:364–369.
59. Kass EH. Bacteriuria and pyelonephritis of pregnancy. *Arch Intern Med*. 1960;105:194–198.
60. Czeizel AE, Rockenbauer M, Sorensen HT, et al. Nitrofurantoin and congenital abnormalities. *Eur J Obstet Gynecol Reprod Biol*. 2001;95:119–126.
61. Goldberg O, Moretti M, Levy A, et al. Exposure to nitrofurantoin during early pregnancy and congenital malformations: a systematic review and meta-analysis. *J Obstet Gynaecol Can*. 2015;37:150–156.
62. Ailes EC, Gilboa SM, Gill SK, et al. Association between antibiotic use among pregnant women with urinary tract infection in the first trimester and birth defects, national birth defects prevention study 1997 to 2011. *Birth Defects Res A Clin Mol Teratol*. 2016;106:940–949.
63. ACOG Committee Opinion No. 404. Sulfonamides, nitrofurantoin and risk of birth defects. *Obstet Gynecol*. 2011;117:1484–1485.
64. van de Mheen L, Smits SM, Terpstra WE, et al. Haemolytic anaemia after nitrofurantoin treatment in a pregnant woman with G6PD deficiency. *BMJ Case Rep*. 2014;10.1135/bcr-2013-010087.
65. Zao J, Koren G, Bozzo P. Using nitrofurantoin while breastfeeding a newborn. *Can Fam Physician*. 2014;60:539–540.
66. Raz R. Fosfomycin: an old–new antibiotic. *Clin Microbiol Infect*. 2012;18:4–7.
67. Liu HY, Lin HC, Lin YC, et al. Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan. *J Microbiol Immunol Infect*. 2011;44:364–368.
68. Butcu M, Akcay SS, Inan AS, et al. In vitro susceptibility of enterococci strains isolated from urine samples to fosfomycin and other antibiotics. *J Infect Chemother*. 2011;17:575–578.
69. Shrestha NK, Tomford JW. Fosfomycin: a review. *Infect Dis Clin Pract*. 2001;10:255–260.
70. Rigsby RE, Fillgrove KL, Beihoffer LA, et al. Fosfomycin resistance proteins: a nexus of glutathione transferases and epoxide hydrolases in a metalloenzyme superfamily. *Methods Enzymol*. 2005;401:367–379.
71. UpToDate: Fosfomycin Drug Information. 2013. http://www.uptodate.com/contents/fosfomycin-drug-information. Accessed March 2013.
72. Falagas ME, Vouloumanou EK, Togia AG, et al. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2010;65:1862–1877.
73. Pullukcu H, Tasbakan M, Sipahi OR, et al. Fosfomycin in the treatment of extended spectrum beta-lactamase—producing *Escherichia coli*—related lower urinary tract infections. *Int J Antimicrob Agents*. 2007;29:62–65.
74. Rodriguez-Bano J, Alcala JC, Cisneros JM, et al. Community infections caused by extended-spectrum beta-lactamase–producing *Escherichia coli*. *Arch Intern Med*. 2008;168:1897–1902.
75. Oteo J, Bautista V, Lara N, et al. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. *J Antimicrob Chemother*. 2010;65:2459–2463.
76. Sen V, Aydogdu O, Bozkurt I, et al. The use of prophylactic single-dose fosfomycin in patients who undergo transrectal ultrasound-guided prostate biopsy: A prospective, randomized, and controlled clinical study. *Can Urol Assoc J*. 2015;9:E863–E867.
77. Rosales MJ, Vega F. Anaphylactic shock due to fosfomycin. *Allergy*. 1998;53:905–906.
78. Reeves DS. Treatment of bacteriuria in pregnancy with single dose fosfomycin trometamol: a review. *Infection*. 1992;20(suppl 4):S313–S316.
79. UpToDate: methenamine drug information. 2013. http://www.uptodate.com/contents/methenamine-drug-information. Accessed March 2013.
80. Gleckman R, Alvarez S, Joubert DW, et al. Drug therapy reviews: methenamine mandelate and methenamine hippurate. *Am J Hosp Pharm*. 1979;36:1509–1512.
81. Duca C, Scudi J. Some antibacterial properties of mandelamine. *Proc Soc Exp Biol Med*. 1947;66:123–126.
82. Klinge E, Männistö P, Mäntylä R, et al. Pharmacokinetics of methenamine in healthy volunteers. *J Antimicrob Chemother*. 1982;9:209–216.
83. Mayrer AR, Andriole VT. Urinary tract antiseptics. *Med Clin North Am*. 1982;66:199–209.

84. Allgen L-G, Holmberg G, Persson B, et al. Biological fate of methenamine in man. *Acta Obstet Gynecol Scand*. 1979;58:287–293.
85. Knoefel P, Huang K. Biochemorphology of renal tubular transport: hippuric acid and related substances. *J Pharmacol Exp Ther*. 1959;126:296–303.
86. Musher DM, Griffith DP. Generation of formaldehyde from methenamine: effect of pH and concentration, and antibacterial effect. *Antimicrob Agents Chemother*. 1974;6:708–711.
87. Musher D, Griffith D, Richie Y. The generation of formaldehyde from methenamine. *Invest Urol*. 1976;13:380–382.
88. Cronberg S, Welin C-O, Henriksson L, et al. Prevention of recurrent acute cystitis by methenamine hippurate: double blind controlled crossover long term study. *Br Med J (Clin Res Ed)*. 1987;294:1507–1508.
89. Harding GK, Ronald AR. A controlled study of antimicrobial prophylaxis of recurrent urinary infection in women. *N Engl J Med*. 1974;291:597–601.
90. Brumfitt W, Cooper J, Hamilton-Miller J. Prevention of recurrent urinary infections in women: a comparative trial between nitrofurantoin and methenamine hippurate. *J Urol*. 1981;126:71–74.
91. Vainrub B, Musher DM. Lack of effect of methenamine in suppression of, or prophylaxis against, chronic urinary infection. *Antimicrob Agents Chemother*. 1977;12:625–629.
92. Kevorkian CG, Merritt JL. Llstrup DM. Methenamine mandelate with acidification: an effective urinary antiseptic in patients with neurogenic bladder. *Mayo Clin Proc*. 1984;59:523–529.
93. Ross RR, Conway GF. Hemorrhagic cystitis following accidental overdose of methenamine mandelate. *Am J Dis Child*. 1970;119:86–87.
94. Kasanen A, Mustakallio E, Koskinen EH, et al. Methenamine hippurate in the treatment of urinary tract infections. *Ann Clin Res*. 1974;6:279–284.
95. UpToDate: Methenamine: Drug information. http://www.uptodate.com/contents/methenamine-drug-information. Accessed March 2018.

38 Topical Antibacterials

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SHORT VIEW SUMMARY

- Topical antimicrobial agents include topical antibacterials, such as mupirocin, clindamycin, and metronidazole, and topical antiseptics, such as chlorhexidine gluconate (CHG), alcohol, and povidone-iodine.
- CHG is available in impregnated cloths for bathing, in impregnated sponges and gels for vascular catheter dressing sites, and as a liquid solution for skin site preparation or washing. Preparations that combine CHG with 70% alcohol are recommended for skin site antisepsis in surgical procedures, for vascular access placement, and for blood culture phlebotomy.
- Daily bathing of critically ill patients with CHG-impregnated cloths has been shown to decrease the subsequent development of multidrug-resistant organism colonization and bloodstream infections.
- Topical mupirocin is available for intranasal use and in cream formulations for use on skin.
- Topical mupirocin can be used to treat impetigo.
- Intranasal mupirocin for decolonization may be beneficial as a preventive strategy for surgical site infections in patients undergoing cardiac surgery, joint replacement surgery, and neurosurgery.
- Topical mupirocin applied to the exit site of hemodialysis catheters is recommended for prevention of bloodstream infection.
- Topical povidone-iodine applied to the hemodialysis catheter exit site may also be beneficial in prevention of bloodstream infections.
- Topical mupirocin applied to peritoneal dialysis exit sites may be beneficial in preventing peritoneal catheter site infection and peritonitis.
- Intranasal mupirocin and CHG bathing have been used as a decolonization regimen in outpatients with recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections and in critically ill inpatients for prevention of hospital-acquired infection.
- The optimal decolonization regimen for MRSA is still not known, and no definitive recommendations on when to attempt decolonization are currently available.
- The cornerstone of management of acne is topical combination therapies that include a benzoyl peroxide and an antimicrobial, such as topical clindamycin or erythromycin.

Topical antibacterial therapy has an important but often undervalued role in the prevention and management of specific infections. Topical antibacterial agents can be subdivided into two types: topical antimicrobials and topical antiseptics. The topical *antimicrobial* agents usually have a primary target site and mechanism of action. They include bacitracin, clindamycin, erythromycin, metronidazole, mupirocin, neomycin, and retapamulin, and they may be administered concomitantly with other systemic antimicrobial agents. Topical antimicrobials have been used to prevent wound infections, treat superficial skin and soft tissue infections (SSTIs), and eradicate carriage of undesirable bacteria, such as *Staphylococcus aureus*. Moreover, these agents may be used to prevent postoperative infections and catheter-related infections in certain patient populations. The topical *antiseptics* (such as chlorhexidine gluconate [CHG], povidone-iodine, and alcohol) have multiple target sites of action against bacteria and are sometimes referred to as biocides.[1] For the purposes of this chapter, the term *topical antibacterials* will refer to both types of agents.

Topical antibacterial therapy has several potential advantages over oral or parenteral antibacterial administration in specific clinical settings (Table 38.1).[2] After the application of small amounts directly to an infection or wound, very high local drug concentrations are achieved, levels that may be toxic if delivered systemically. When administered topically, these agents first enter the skin (the first target organ), and then a variable quantity is distributed throughout the body and finally eliminated. Concentrations of a topical antibacterial decline from the skin surface to the subcutis (after systemic administration, the opposite occurs) (Fig. 38.1).[3] Therefore, topical administration is favored if the pathologic process is in the epidermis or papillary dermis because the highest doses are delivered directly to the site of infection. For infection in the lower dermis or subcutis, it is necessary to determine whether a topically administered antibacterial provides the drug concentrations necessary to effectively eradicate the infection. Topical preparations formulated to contain combinations of topical antibacterial agents may offer the benefits of synergism and delay the selection of resistant microorganisms. In this chapter, we review the general uses of topical antibacterial agents in the therapy and prevention of infections. Topical agents are also effective in treating eye (see Chapters 111 through 116) and ear (see Chapter 61) infections.

GENERAL USES OF TOPICAL ANTIBACTERIALS

Skin Disinfection

Skin disinfection is a critical component of safe and effective patient care and includes disinfection of patients' skin to provide a sterile environment for procedures, and disinfection of health care workers' skin to prevent transmission of pathogenic bacteria through contact with patients. Some topical antibacterial agents, in particular the topical antiseptics, are very effective at decreasing the number of bacteria on the skin. The ideal antiseptic agent should have the following properties: a broad antimicrobial spectrum; rapid bactericidal activity; persistent activity on the skin; an absence of irritating, allergic, or toxic reactions; an absence of systemic absorption; activity in the presence of body fluids (e.g., blood); and cosmetic acceptance.[2] Unfortunately, no single compound meets all these criteria. However, depending on the specific clinical situation, only certain properties may be required. For example, for repeated hand washing (e.g., by medical personnel), lack of irritation and persistence of activity are essential properties. In contrast, for the preparation of operative sites, rapid bactericidal activity is required.

Several topical antiseptic agents are used as skin disinfectants. Hexachlorophene is no longer used as a skin disinfectant for many reasons. The iodophors, in particular povidone-iodine, are widely used as skin antiseptics. Povidone-iodine is an organic complex of polyvinylpyrrolidone and triiodine ions (the antimicrobial component) that slowly liberates iodine on reduction. Iodophors have a broad antimicrobial spectrum; however, antibacterial activity does not persist for prolonged periods on the skin, in wounds, or on mucous membranes, and iodophors

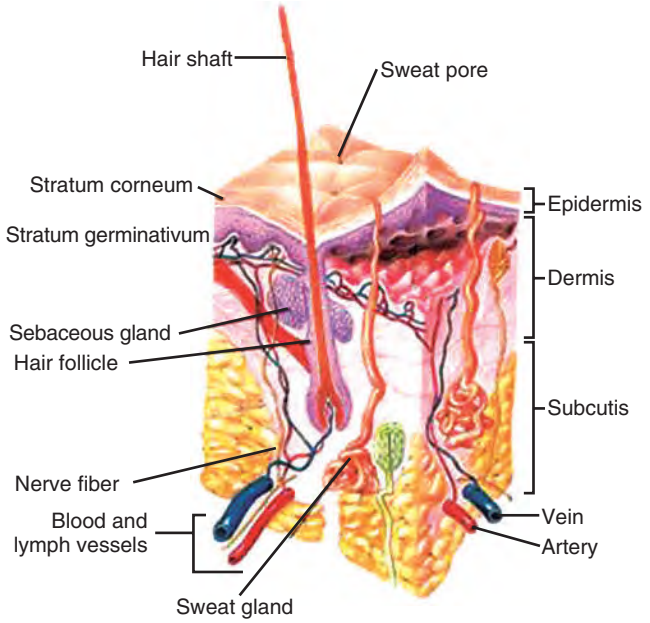

FIG. 38.1 Skin structures.

TABLE 38.1 Advantages of Topical Antibacterial Therapy

Ease of administration
Lower potential for adverse reactions
Lower risk of noncompliance
Delivery of high drug concentrations to site of infection
Decreased risk of bacterial resistance or antimicrobial cross-resistance
Cost savings (depending on agent used)

may be inactivated by blood and body fluids. Their microbicidal effects are the result of cell wall penetration, oxidation, and substitution of microbial contents with free iodine. Povidone-iodine's antibacterial effect is directly related to its desiccation, or drying, after application. Failure to allow the product to dry completely will result in incomplete antisepsis. For proper effect, povidone-iodine must be applied properly, according to the manufacturer's instructions, and allowed to dry thoroughly. Povidone-iodine has been widely used for many years in preoperative skin preparation, preparation of skin for blood culture phlebotomy, certain catheter placements, hand scrubbing, and the treatment and prevention of skin infections.[2]

Povidone-iodine in a 5% cream preparation has been studied for its in vitro activity against various strains of *S. aureus,* including methicillin-resistant strains (MRSA) and mupirocin-resistant strains. It has also been evaluated for its bioavailability in human nasal secretions and has demonstrated rapid bactericidal activity and good bioavailability within the human nares.[4] The cream formulation may play a role in the prevention of infection and eradication of nasal colonization by *S. aureus.*

Alcohols are rapidly bactericidal, but older preparations were not widely adopted because of their transient antiseptic action, local irritation, and excessive drying, especially when associated with repeated use. Over the last 15 years, newer waterless, alcohol-based hand hygiene products have been brought to market in the United States. These products contain 70% alcohol as the active antiseptic ingredient, and also contain emollients to minimize or eliminate the drying or irritating side effects. Alcohol-based hand sanitizers also differ from older preparations in that their antiseptic action is far more prolonged. Because these products are waterless, and there is no need for a sink or paper towels, alcohol-based hand sanitizers can be made widely available in and around patient care areas, which encourages more widespread use. Current guidelines on hand hygiene recommend these products over soap and water as the preferred method for cleaning unsoiled hands before and after patient encounters.[5]

Chlorhexidine, a cationic bisbiguanide that achieves its antiseptic activity by causing disruption of microbial cell membranes and precipitation of cell contents, is an ideal agent for skin cleaning and surgical scrubs. Its noteworthy properties include persistent activity on the skin when used regularly, rapid bactericidal activity, a broad antibacterial spectrum, little evidence of irritation or allergy, activity in the presence of body fluids, and minimal absorption. Chlorhexidine-containing products have become more widely available in the United States since the US Food and Drug Administration (FDA) approved a 2% tincture of a chlorhexidine gluconate (CHG) preparation for use as a skin antiseptic in 2000. CHG formulations containing 0.5% to 0.75% chlorhexidine are more effective than plain soap and water but less effective than preparations containing 4% chlorhexidine.[6] Preparations containing 2% chlorhexidine are slightly less effective than those containing 4%. When 0.5% to 1% CHG is combined with 70% alcohol-based preparations, the greatest antibacterial activity can be observed. In a study comparing 2% chlorhexidine, povidone-iodine, and 70% alcohol for sterile skin preparation of central venous and arterial catheter sites, the 2% chlorhexidine lowered rates of subsequent bloodstream infections (BSIs) significantly more than the other two preparations.[6] Chlorhexidine-containing preparations are not currently recommended for use in children 2 months of age or younger or in surgery involving the inner or middle ear because of the ability of chlorhexidine to cause ototoxicity. Current guidelines for the prevention of vascular catheter–related infections recommend CHG-containing products for preparation of the skin before catheter insertion.[7] Several additional uses of CHG-containing products are discussed later and include use as skin preparation before blood culture phlebotomy, use as a skin antiseptic agent in the preoperative setting, and use as a skin wash to prevent hospital-acquired infections (HAIs) in critically ill hospitalized patients.

Triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether) is a synthetic bisphenol active against a broad range of gram-positive and gram-negative bacteria. It is a biocide that had been used extensively for many years in dental hygiene products and soaps and has been incorporated into plastic kitchenware products, toys, and tea towels.[8,9] In September 2016, the FDA removed triclosan and triclocarban from over-the-counter hand and body washes owing to lack of efficacy and concerns about systemic absorption and development of resistance; however, they are still present in many products.[10] A summary of the antimicrobial spectrum and characteristics of antiseptic agents is provided in Table 38.2.

Prophylaxis of Infection in Clean Wounds

When a wound leads to disruption of epidermal integrity (e.g., secondary to abrasions, cuts, or bites), the application of a topical antibacterial agent to prevent infection from developing can be considered. However, no antibacterial formulation has ever been proven to be efficacious in the prophylaxis of clean wounds because so few clean wounds become infected. Studies of topical preparations (e.g., neomycin alone or in combination with bacitracin, polymyxin, or both) have shown efficacy in the prevention of infection in some circumstances, although these studies have been criticized because of the absence of control groups.[11] Controlled studies are unlikely to ever be performed, and the effects of these agents on the microbiome are not known.

To avoid the difficulties in performing a large randomized controlled trial, a human skin infection model was developed to test the efficacy of topical antibiotic formulations in the prophylaxis of minor skin infections.[11] After the induction of abrasion-type wounds in human volunteers, the wounds were inoculated with either 10^5 organisms of *S. aureus* or 10^7 organisms of *Streptococcus pyogenes* and covered with an impermeable dressing for 6 hours. Both neomycin and bacitracin were more effective in preventing infection with both *S. aureus* and *S. pyogenes* than the placebo ointment vehicle. The treated wounds did not develop pus and reepithelialized within 3 to 5 days. Other investigators have also found that the use of either topical neomycin-bacitracin-polymyxin ointment or bacitracin alone enhanced the epidermal healing of wounds[12] and significantly reduced streptococcal skin colonization and the subsequent infection of small skin trauma in children.[13] Despite these studies, the efficacy of topical antibacterials in the prevention of infections in clean wounds and wound healing remains uncertain. The

TABLE 38.2 Antimicrobial Spectrum and Characteristics of Antiseptic Agents

GROUP	GRAM-POSITIVE BACTERIA	GRAM-NEGATIVE BACTERIA	MYCOBACTERIA	FUNGI	VIRUSES	SPEED OF ACTION	COMMENTS
Alcohols	+++	+++	+++	+++	+++	Fast	Optimum concentration 60%–95%; no persistent activity
Chlorhexidine (2% and 4% aqueous)	+++	++	+	+	+++	Intermediate	Persistent activity; rare allergic reactions
Iodine compounds	+++	+++	+++	++	+++	Intermediate	Causes skin burns; usually too irritating for hand hygiene
Iodophors	+++	+++	+	++	++	Intermediate	Less irritating than iodine; acceptance varies
Phenol derivatives	+++	+	+	+	+	Intermediate	Activity neutralized by nonionic surfactants
Quaternary ammonium compounds	+	++	–	–	+	Slow	Used only in combination with alcohols; ecologic concerns

[a]Hexachlorophene is not included because it is no longer an accepted ingredient of hand disinfectants.
+++, Excellent; ++, good but does not include the entire bacterial spectrum; +, fair; –, no activity or not sufficient.

use of topical antibacterials in superficial wounds for a few days, until the integrity of the epidermis is reestablished, has been recommended because the longer the epidermal barrier remains defective, the more likely it is that infection will occur; however, the strength of the evidence around this recommendation is weak.

The use of topical antibacterials in chronic nonhealing, noninfected wounds, such as pressure ulcers, has been recommended by the US Agency for Health Care Policy and Research.[14] The goal of such therapy is to decrease the bacterial burden in these wounds and possibly to promote healing. However, there is no substantial evidence in the published medical literature that this goal can be achieved.[15] A Cochrane review from 2014 included 45 randomized controlled trials with 4486 participants and found no evidence for the use of topical antiseptics to promote healing of chronic venous leg ulcers.[16] A clinical practice guideline from the American College of Physicians on treatment of pressure ulcers does not recommend use of topical antiseptic or antibiotic agents.[17] Moreover, the chronic use of topical antibacterials may be expected to promote bacterial resistance and should be avoided. None of the currently marketed topical antibacterials has been labeled for use specifically in the setting of chronic nonhealing wounds.[15] Therefore the use of topical antibacterials for chronic nonhealing wounds should be discouraged.

Prophylaxis of Recurrent Skin and Soft Tissue Infections

Some patients with recurrent furuncles, carbuncles, and other SSTIs caused by *S. aureus* may have persistent nasal carriage of this organism. It has been suggested that eradication of *S. aureus* from the nares could reduce the recurrence of these infections. One randomized trial treated such patients with a 5-day course of intranasal mupirocin and then randomized half the patients to receive successive monthly therapy for 1 year, and half to receive a placebo.[18] Intranasal mupirocin reduced the recurrence of furunculosis by approximately 50% in study subjects who were colonized with *S. aureus* in their nares. The small size of the study precluded the authors from making definitive recommendations for the management of recurrent furunculosis and folliculitis in staphylococcal carriers.

A 2011 open-label trial sought to determine whether there is benefit to topical mupirocin alone or in combination with other strategies, in the prevention of recurrent SSTIs caused by *S. aureus*. Fritz and colleagues[19] enrolled 300 patients with community-associated SSTIs and *S. aureus* colonization of the nares, axilla, or inguinal folds and randomly assigned them to one of four groups: no treatment, education only; twice-daily intranasal mupirocin ointment for 5 days; twice-daily intranasal mupirocin plus daily chlorhexidine body washes for 5 days; or twice-daily intranasal mupirocin plus daily 15-minute dilute bleach water soaks (one-fourth cup of bleach per tub of water). All groups received education about personal and household hygiene. Decolonization with mupirocin alone or in combination with chlorhexidine or bleach baths was more effective than education alone at eradicating colonization at 1 month (56%, 55%, and 63% vs. 38%, respectively). However, at 4 months the only regimen more effective than education alone in eradicating colonization was mupirocin plus bleach baths (71% vs. 48%). Recurrent SSTI was common, occurring in 20% of participants at 1 month and 36% of participants at 4 months, suggesting that factors other than endogenous colonization play a role in MRSA infection.[19] Many practitioners, including us, are now recommending dilute bleach baths twice a week for patients with recurrent community-associated MRSA infections. The bath is prepared by adding one-quarter cup of bleach to a bathtub of water. The patient must soak in the bath for 15 minutes twice weekly.[19] Nasal mupirocin is being used as part of a prophylactic regimen that may also include topical CHG washes, bleach bathing, oral antimicrobials, or any combination of the three, as a skin decolonization regimen. This is discussed in further detail later.

Prophylaxis of Infection in Operative Wounds

With more than 30 million surgical procedures performed annually in the United States, surgical site infections (SSIs) have become the most common and costly HAI. Current estimates suggest that 2% to 5% of the 30 million patients will develop an SSI. Most SSIs are caused by endogenous microbiota, including *S. aureus*. *S. aureus* is the etiologic agent of 20% to 30% of all SSIs. SSI prevention strategies have focused on (1) MRSA decolonization; (2) optimal methods to decrease bioburden on the host's skin before the procedure; and (3) determining the best antiseptic agent for skin preparation of the surgical site.

MRSA Decolonization

Several studies have been performed in a variety of surgical patients to evaluate the effectiveness of preoperative decolonization with intranasal mupirocin, alone or in combination with other products, on the subsequent rate of postoperative SSIs.

Universal Decolonization

The first large randomized controlled, multicenter trial examining use of intranasal mupirocin versus placebo enrolled 4030 patients undergoing general, cardiothoracic, neurosurgical, and gynecologic surgical procedures.[20] Of the 3864 patients included in the intention-to-treat analysis, 2.3% of mupirocin-treated patients developed an SSI, compared with 2.4% of the placebo recipients. In a secondary analysis of 891 patients who were noted to have *S. aureus* nasal carriage before surgery, those patients treated with mupirocin had a subsequent SSI rate of 4%, compared with their placebo-treated counterparts, who had a 7.7% rate of subsequent infection, a difference that was not statistically significant. The lack of a statistically significant outcome in this study resulted in part from the fact that the sample size calculation had 85% power to detect a relative reduction of 50% in the rate of *S. aureus* SSIs.[21]

Targeted Decolonization for Patients Who Screen Positive for *Staphylococcus aureus*

A study examined the impact of preoperative *S. aureus* screening and targeted decolonization on the incidence of postoperative MRSA colonization, intensive care unit (ICU) MRSA transmission, and SSIs in cardiac surgery patients. During the intervention period, subjects underwent nasal screening for methicillin-susceptible *S. aureus* (MSSA) and MRSA with polymerase chain reaction (PCR) assay, and colonized patients received intranasal mupirocin twice daily and chlorhexidine baths daily for 5 days. There were 2826 patients in the preintervention period and 4038 patients in the intervention period. Patients found to be colonized with MRSA received vancomycin plus cefazolin for surgical prophylaxis. The authors found that the intervention patients had risk-adjusted reductions in MRSA colonization. Increased duration of preoperative decolonization therapy was associated with decreased postoperative MRSA colonization (odds ratio, 0.73; 95% confidence interval [CI], 0.53 to 1.00; $P = .05$). This study provided evidence that preoperative *S. aureus* screening with targeted decolonization was associated with reduced MRSA colonization, transmission, and SSIs.[22]

A multicenter US study evaluated whether the implementation of MRSA decolonization as part of an evidence-based bundle was associated with a lower risk of *S. aureus* SSIs in patients undergoing cardiac operations or hip or knee arthroplasties. Patients whose preoperative nares screens were positive for MRSA or MSSA were asked to apply mupirocin intranasally twice daily for up to 5 days and to bathe daily with chlorhexidine-gluconate for up to 5 days before their operations. MRSA carriers received vancomycin and cefazolin or cefuroxime for perioperative prophylaxis; all others received cefazolin or cefuroxime. Patients who were MRSA negative and MSSA negative bathed with CHG the night before and the morning of their operations. Rates of SSIs were collected during the preintervention and postintervention periods. The primary outcome was complex *S. aureus* SSIs. These occurred in 36 of 10,000 operations in the preintervention period and 21 of 10,000 operations in the intervention period (relative risk [RR], 0.58; 95% CI, 0.37 to 0.92). The rates of complex *S. aureus* SSIs decreased significantly for hip or knee arthroplasties (difference per 10,000 operations, −17 [95% CI, −39 to 0]). There was not a demonstrated statistically significant decrease in SSIs among the patients undergoing cardiac surgery in this study (difference per 10,000 operations, −6 [95% CI, −48 to 8]; RR, 0.86 [95% CI, 0.47 to 1.57]).[23]

A meta-analysis of 17 studies assessed nasal decolonization (5 were randomized controlled trials and 12 were quasiexperimental studies); 10 studies included cardiac operations, 3 assessed joint arthroplasties, and 4 assessed other orthopedic procedures. In 16 of the 17 studies, mupirocin was used for decolonization, whereas in 1 study nasal CHG was used. A total of 11 studies examined decolonization regardless of whether the participants carried *S. aureus* in their nares. Nasal decolonization was associated with a significant decrease in *S. aureus* SSIs (pooled RR, 0.4; 95% CI, 0.29 to 0.55). In contrast, 6 other studies were designed to decolonize only patients who carried *S. aureus* in their nares. The pooled effect estimate in these 6 studies indicated that this approach was also associated with a significant decrease in *S. aureus* SSIs (RR, 0.36; 95% CI, 0.22 to 0.57). Nasal decolonization plus skin decontamination with CHG or triclosan was assessed in 6 studies. The pooled effect estimate showed protection against *S. aureus* SSIs (RR, 0.29; 95% CI, 0.19 to 0.44). None of the studies compared nasal decolonization alone with nasal decolonization plus skin decontamination.[24]

In summary, the data show that nasal decolonization with mupirocin plus skin decontamination with CHG decreases the risk of *S. aureus* SSIs in both patients with and those without *S. aureus* colonization of nasal passages. Most studies have been performed in cardiac and orthopedic populations. We believe that this is an appropriate strategy and has been considered both cost-effective and clinically effective.

Concerns with mupirocin such as cost and patient compliance (mupirocin must be applied for several days to be effective) have led researchers to seek alternate strategies for nasal decolonization. Povidone-iodine–based ointment for nasal decolonization can be applied 2 hours before surgical incision, and therefore there is less concern regarding patient compliance. A single-center study examined a prospective cohort of patients undergoing elective orthopedic surgery with hardware implantation. Patients were given CHG washcloths and oral rinse and nasal povidone-iodine solution to be used the night before and the morning of scheduled surgery. The SSI rate in the intervention group (1.1%) was significantly lower than in the control group (3.8%).[25]

One randomized trial has performed a head-to-head comparison of mupirocin ointment for 5 days before surgery versus 30-second applications of povidone-iodine 5% solution into each nostril within 2 hours of surgical incision. Both groups also received 2% CHG wipes. In the intention-to-treat analysis, a deep SSI developed after 14 of 855 operations in the mupirocin group and 6 of 842 operations in the povidone-iodine group; *S. aureus* deep SSI developed after 5 operations in the mupirocin group and 1 operation in the povidone-iodine group. This study shows that povidone-iodine may be considered an alternative to mupirocin as part of a multifaceted approach to reduce SSI.[26]

Topical Skin Antisepsis

The routine application of topical antiseptics to the skin before a surgical procedure is a standard practice. The choice of topical antiseptic in this setting has varied in the past. However, several publications and a meta-analysis all have concluded that preoperative skin site preparation with CHG-alcohol preparations are superior to povidone-iodine. In a randomized controlled trial of 849 patients undergoing clean contaminated surgical procedures, the SSI rate was significantly lower in the CHG-alcohol group (9.5%) compared with the povidone-iodine group (16%).[27-29] Chlorhexidine-alcohol may be superior because CHG is not inactivated by blood or serum and has longer residual activity than povidone-iodine. Some experts have suggested that when CHG-alcohol is compared with povidone-iodine plus alcohol, there may be no significant benefit to the CHG-containing product. In a study that compared a povidone-iodine–alcohol preparation with a CHG-alcohol preparation and a standard povidone-iodine paint with an isopropyl alcohol wash in between, researchers determined that SSI rates were the lowest in the period during which the povidone-iodine–alcohol product was in use.[30] A blinded randomized noninferiority trial compared iodine povacrylex–alcohol and chlorhexidine-alcohol for elective clean contaminated colorectal surgery. In the intention-to-treat analysis the use of iodine povacrylex failed to meet criteria for noninferiority for overall SSI prevention compared with chlorhexidine-alcohol.[31] To date, studies have suggested that CHG is superior to povidone-iodine. Whether addition of alcohol to povidone-iodine would make this a product equal to CHG remains debatable. However, studies have shown conflicting results, and therefore more data are needed in order to determine whether povidone-iodine with alcohol is noninferior to CG with alcohol.

Methods to Decrease Bioburden on Skin

The use of chlorhexidine bathing preoperatively, as part of a bundle of interventions, has become a trend in SSI prevention. Patients may be told to bathe the evening before, on the morning of, or on several occasions before the planned surgical procedure. Different CHG-containing products may be used, either a wash or a wipe. Bathing with any antiseptic preparation before surgery has no proven benefit, as concluded in a 2007 Cochrane Database systematic review.[32] A more recent meta-analysis of 16 trials included a total of 17,932 patients; 7952 patients used a chlorhexidine bath, and 9980 patients were allocated to various comparator groups. Overall, 6.8% of patients developed SSI in the chlorhexidine group compared with 7.2% of patients in the comparator groups. Chlorhexidine bathing did not significantly reduce overall incidence of SSI when compared with soap, placebo, or no shower or bath (RR, 0.90; 95% CI, 0.77 to 1.05; $P = .19$).[33] Given that CHG bathing is often part of a several-pronged approach to SSI reduction, it may not be possible to determine its efficacy as a single intervention.

Prophylaxis of Vascular Catheter–Related Infections

The use of topical antibacterial agents to prevent vascular catheter–related infections includes choice of appropriate skin site antiseptic preparation and the use of a topical agent applied to the catheter site as part of line site maintenance. Studies assessing skin site preparation before central venous catheter (CVC) insertion have demonstrated that 2%

CHG-alcohol preparations are superior to povidone-iodine preparations or 70% isopropyl alcohol–only preparations.[6] Current guidelines on the prevention of vascular catheter–related infections recommend CHG-alcohol preparations as the preferred skin site antiseptic.[7] After insertion, guidelines recommend disinfecting catheter hubs, connectors without needles, and injection ports before accessing the catheter with an alcohol-chlorhexidine preparation or 70% alcohol to reduce contamination.

A chlorhexidine-impregnated sponge applied as a standard CVC exit site dressing cover has been shown to reduce BSIs in several studies. A meta-analysis looking at chlorhexidine-impregnated sponge dressings demonstrated that its use was associated with a trend toward reduction of central line–associated bloodstream infections (CLA-BSIs).[33] A large randomized controlled trial comparing the chlorhexidine-impregnated sponge with standard dressings revealed that the impregnated sponge significantly reduced the incidence of CLA-BSIs from 1.3 to 0.4 per 1000 catheter-days.[34] Society guidelines recommend considering the addition of this dressing in several circumstances, including (1) in hospital units or patient populations with CLA-BSI rates higher than the institutional goal, despite compliance with an evidence-based prevention bundle; (2) in patients with limited venous access and a history of recurrent CLA-BSI; or (3) in patients at increased risk for severe sequelae from CLA-BSI, such as patients with a recently implanted intravascular device, prosthetic heart valve, or aortic graft.[7]

More recently, a chlorhexidine-impregnated gel dressing has been developed that allows continuous inspection of the insertion site. No studies have directly compared CHG foam and CHG gel–based dressing. However, a randomized control trial compared CHG-impregnated gel dressings and standard nonchlorhexidine dressings and found that in 1879 patients the rate of vascular catheter–related infection was 67% lower ($P = .0006$). The contact dermatitis rate was 1.1%.[35]

Applying a topical antibacterial agent to the vascular access site to decrease bacterial burden and prevent bacterial colonization of intravascular catheter sites is of unclear benefit. In one prospective evaluation of 827 random catheter insertions in which three regimens of catheter care (neomycin-bacitracin-polymyxin at insertion and every 48 hours vs. iodophor ointment at insertion and every 48 hours vs. no ointment) were used, no differences in catheter-acquired sepsis (2 patients in each group) or local inflammation (38.9% vs. 41.9% vs. 41.7%, respectively) were noted.[36] The only differences were in semiquantitative cultures of catheter tips, with 6 positive cultures in the neomycin-bacitracin-polymyxin group, 10 in the iodophor group, and 18 in the no-treatment group. In contrast, a randomized controlled trial of povidone-iodine in the prevention of infection in subclavian vein hemodialysis (HD) catheters found that povidone-iodine was associated with a significant decrease in the incidence of septicemia (5% vs. 18%; $P < .02$).[37]

Prophylaxis of Peritoneal Dialysis Catheter Infections

Catheter-associated infections in patients undergoing either HD or peritoneal dialysis are one of the most common reasons for hospitalization and catheter removal in this patient population. In patients who undergo peritoneal dialysis, a few strategies have demonstrated efficacy in prophylaxis against exit site and tunnel infections. In the absence of prophylaxis, the average rates of *S. aureus* exit site infections range from 0.34 to 0.41 episodes per patient-year.[38] Patients with *S. aureus* nasal colonization have exit site infection rates that are significantly higher (>0.5 infections per year).[39] Moreover, the rates of peritonitis in patients with one or more positive naris cultures for *S. aureus* have been shown to be significantly higher than they are in patients never colonized (0.24 vs. 0.08 per year).[40] With the use of some prophylaxis regimen, the rates of infection can be reduced to less than half these numbers.[41]

The application of povidone-iodine at the exit site of the peritoneal dialysis catheter was shown to be effective in reducing subsequent infection rates in some published studies.[41] However, this strategy has also failed to demonstrate effectiveness in other published data.[40] The overall effectiveness of povidone-iodine in this setting remains unclear. As discussed earlier, the use of intranasal mupirocin twice daily for 5 days for the treatment of *S. aureus* nasal carriage has been shown to be an effective strategy in decreasing *S. aureus* carriage and catheter infections in patients who are proven nasal carriers.[42-44] The long-term effectiveness of intranasal mupirocin is approximately 60%, and therapy may need to be repeated either monthly or, if routine cultures are performed, whenever cultures are found to be positive for *S. aureus*. In a prospective open trial of intranasal mupirocin, peritoneal dialysis patients were treated with mupirocin when naris cultures were positive for *S. aureus*.[43] Compared with historical control subjects, exit site infections were significantly decreased from 0.22 per patient-year among control subjects to 0.09 per patient-year in the mupirocin-treated patients. Topical intranasal mupirocin also resulted in a significant decrease in the subsequent rates of *S. aureus* peritonitis in this study, although the rates of peritonitis caused by gram-negative organisms increased over the study period. The only randomized, double-blind, placebo-controlled trial of monthly intranasal mupirocin was performed by the Mupirocin Study Group in nine centers throughout Europe.[45] Peritoneal dialysis patients with positive naris cultures for *S. aureus* were randomized to receive twice-daily intranasal mupirocin or placebo for 5 days every 4 weeks and followed for 18 months. Although the rate of *S. aureus* exit site infections was significantly lower in the mupirocin group in this study, the total rate of exit site infections, tunnel infections, and peritonitis was not significantly different between treated and placebo recipients. Of note, in a cost-effectiveness analysis, it was not cost-effective to use prophylactic topical intranasal mupirocin in chronic peritoneal dialysis patients.[46]

Another prophylactic strategy is the application of topical mupirocin to the exit site as part of the routine daily care of the peritoneal dialysis catheter. In a prospective, randomized study comparing oral rifampin with topical mupirocin applied daily to the exit site, the rates of infection were compared with those of historical control groups.[47] The rates of *S. aureus* exit site infections, tunnel infections, peritonitis, and catheter loss caused by *S. aureus* infections were not statistically different between the two treatment groups, but they were significantly lower than those in the historical control group. In another prospective, controlled, historical study, in which a group of peritoneal dialysis patients were treated with topical mupirocin at the exit site three times weekly,[48] there was a significant reduction in *S. aureus* exit site infections (21 vs. 3 episodes) and *S. aureus* peritonitis (35 vs. 11 episodes); however, the patients were not screened for *S. aureus* carrier status. In several smaller studies (none of which were randomized, placebo controlled, or blinded), topical mupirocin was applied to the exit site either daily or three times weekly, and the results were similar with respect to decreased rates of peritoneal dialysis catheter–related infections.[40,49,50] A more recently published experience also advocated exit site mupirocin in peritoneal dialysis patients.[49] However, no cost-effectiveness analyses have been performed for the use of topical mupirocin in this patient population.

A systematic review looked at seven studies that compared topical gentamicin and topical mupirocin for prevention of peritoneal dialysis–associated exit site infections. There were 458 patients in the mupirocin group and 448 in the gentamicin group. The risk of gram-positive exit site infection was similar between the groups. The gram-negative exit site infection rate was higher in the mupirocin group (RR, 2.125; $P = .037$). Of the 7 studies, 6 also assessed the risk of bacterial peritonitis. There was no difference in the gram-positive or gram-negative peritonitis rate.[51]

We agree with the International Society of Peritoneal Dialysis 2016 guidelines, which recommend daily use of either topical gentamicin or mupirocin cream or ointment at the peritoneal dialysis exit site.[52]

Prophylaxis of Hemodialysis Catheter Infections

Catheter-associated BSI rates in the HD patient population remain high, even as BSI rates in hospitalized patients continue to decline.[53] Several potential prophylactic strategies have been evaluated in the HD catheter population, some of which include the application of topical antibacterial agents, including topical mupirocin, topical povidone-iodine, or topical Polysporin, to the exit site, and intranasal mupirocin.[40] Several studies have looked at the use of topical mupirocin at the catheter exit site. Studies of topical mupirocin used at the HD catheter exit site have shown decreased incidence rates of exit site infections and bacteremia and longer times to onset of bacteremia.[54] In one such randomized, controlled, open-label trial of topical exit site mupirocin application in

patients with tunneled, cuffed HD catheters, a total of 50 HD patients were randomized to topical mupirocin applied to the catheter exit site three times weekly versus no treatment.[54] The rates of *S. aureus* nasal carriage in the two groups were similar. Compared with control subjects, the mupirocin-treated patients had significantly fewer incidents of catheter-related bacteremia (7% vs. 35%) and had a longer time interval to the first incident of bacteremia. Median catheter survival was also significantly longer in the treated group.[54] A Cochrane Database systematic review in 2010 concluded that topical mupirocin reduced HD catheter–associated BSIs.[55] The study determined that there was insufficient evidence to support the use of povidone-iodine ointment, Polysporin ointment, honey, or a variety of topical catheter site dressings in prevention of BSI. Topical mupirocin is an effective strategy in prevention of bacteremias in HD catheter patients.

Although not determined to be definitively effective in a Cochrane Database review, povidone-iodine ointment is recommended in the 2011 Centers for Disease Control and Prevention guidelines for prevention of catheter-related BSIs in HD patients.[7] In a randomized open-label study of 129 patients, exit site infection and bacteremia were significantly higher in the control group compared with patients provided povidone-iodine ointment.[37] Another single-site, prospective, randomized, open-label study evaluated the use of povidone-iodine at the exit site of the HD catheter, along with a sterile dressing, versus sterile dressing alone.[56] At the onset of this study, 22% of the patients in the treatment group and 32% of those in the placebo group were positive for *S. aureus* nasal carriage. The incidence of bacteremia was significantly higher in the control group compared with those treated with povidone-iodine—17% versus 2% incidence. Similar results were found with respect to exit site infections in this study. The value of povidone-iodine ointment is likely real, and additional studies in which povidone-iodine ointment is used as part of catheter site care are needed. We believe that topical mupirocin is an effective strategy in prevention of bacteremias in HD catheter patients; however, a contrary view is taken by the authors of Chapter 300, who do not recommend topical mupirocin around tunneled HD catheter exit sites. These differences in approach reflect the paucity of truly comparative data.

The efficacy of intranasal mupirocin as a preventive strategy for HD catheter bacteremias or exit site infections has been studied in several published trials. However, topical mupirocin at the exit site is currently recommended and preferred over intranasal mupirocin. In one study, intranasal mupirocin was used three times daily for 2 weeks after catheter insertion, followed by three times weekly as a maintenance regimen, versus placebo.[57] All patients were positive for *S. aureus* nasal carriage before enrollment and were followed for 9 months. The authors observed a significant decrease in nasal colonization in the mupirocin-treated group and a significant decrease in the rate of *S. aureus* infections. However, the rates of *S. aureus* bacteremia did not differ between the treated group and the placebo recipients. A subsequent prospective open-label study performed by the same group used intranasal mupirocin in HD patients three times weekly for 6 months and then once weekly for 6 months.[58] The study patients were compared with historical control subjects and were found to have had a statistically significant decrease in *S. aureus* bacteremia over the study period. Another prospective open trial assessing intranasal mupirocin applied once weekly in HD patients showed significantly decreased rates of *S. aureus* bacteremia in the mupirocin-treated study patients compared with historical control subjects.[59] A single cost-effectiveness analysis of intranasal mupirocin in HD patients suggested that such a strategy was cost-effective.[60]

Prophylaxis of Health Care–Associated Infections

Despite ongoing prevention efforts over the last decade across the United States and globally, HAIs continue to result in morbidity, mortality, and increased costs. Twenty percent of HAIs are acquired in the critical care setting, and risk of HAI increases with length of critical care stay.[61] The three most common critical care HAIs are catheter-associated urinary tract infection (CA-UTI), CLA-BSI, and ventilator-associated lower respiratory tract infections. Over the last decade, national device-associated HAI rates have declined somewhat, in particular because of implementation of bundled prevention strategies. The use of daily CHG bathing has been proved to be an effective method of both reducing the development of HAIs and preventing colonization of critical care patients with multidrug-resistant organisms (MDROs).[62-65]

In the largest published prospective study to date, daily bathing with 2% CHG–impregnated washcloths was implemented in a multicenter, cluster-randomized, nonblinded crossover trial.[62] Primary outcomes included incidence rates of MDRO acquisition and rates of CLA-BSIs. Nine critical care settings or bone marrow transplant units were used. Patients were randomized to either daily bathing with CHG for 6 months or use of a nonantimicrobial bathing cloth, and in the second 6 months the daily bathing product was alternated. More than 7700 patients were enrolled, and a 23% reduction in MDRO acquisition rate was found. The MDRO acquisition rate was 5.1 cases per 1000 patient-days in the CHG bathing group, compared with 6.6 cases per 1000 patient-days in the standard bathing group; this was statistically significant. CHG-bathed patients had a CLA-BSI rate of 4.78 per 1000 patient-days, compared with 6.6 CLA-BSIs per 100 patient-days in the control group. This translated to a 28% lower rate of CLA-BSIs in those patients bathed with CHG, and this result was also statistically significant.

A 2012 meta-analysis to assess the efficacy of daily CHG bathing in reducing HAI occurrences in ICU patients concluded that there was benefit to the practice.[63] One randomized and 11 nonrandomized trials were included in the analysis. CHG bathing led to a significant reduction in BSI rates and CLA-BSI rates, with a pooled odds ratio of 0.44. The authors noted that there was a wide variation across studies with respect to the type of product and concentration of CHG, along with differences in use of other infection-control practices, such as active surveillance cultures, nasal mupirocin use, and enhanced hand hygiene. Of note, adverse events were extraordinarily rare.

A more recent cluster-randomized crossover study of 9340 patients admitted to five ICUs in a tertiary medical center in the United States used a 10-week period of bathing with 2% CHG washcloths, a 2-week washout period, and then 10 weeks of bathing with nonbacterial washcloths.[66] The primary outcome was a composite of CLA-BSI, CA-UTI, ventilator-associated pneumonia (VAP), and *Clostridioides difficile* (formerly *Clostridium difficile*) rate. The study found no reduction in the primary outcome. However, of note, this study had low rates of HAIs and used a composite end point instead of looking at only CLA-BSI.

In summary, most studies have shown that bathing patients in the ICU with CHG decreases rates of CLA-BSI, acquisition of MRSA and vancomycin-resistant enterococcus (VRE), and blood culture contamination rates. It is unclear what the impact of CHG bathing is on CA-UTI, VAP, and *C. difficile* rates.

Researchers have also addressed the question of whether targeted or universal decolonization to prevent ICU infection or colonization is effective.[64] Forty-three hospitals with 74 ICUs participated in a cluster-randomized trial assessing three strategies: MRSA screening and isolation (standard practice), targeted decolonization (for patients who were MRSA-screen positive), or universal decolonization. Patients in the universal decolonization study group were not assessed for MRSA carrier state. Universal decolonization included daily CHG bathing for the entire ICU stay plus 5 days of nasal mupirocin on admission for all patients. Compared with baseline preintervention rates, universal decolonization reduced MRSA acquisition rates and rates of BSIs caused by any pathogen more often than either standard practice or targeted decolonization. The cost of universal decolonization was approximately $40 per patient. Researchers determined that 181 patients would need to be decolonized to prevent one MRSA infection, whereas 54 patients would require decolonization to prevent one ICU BSI. Because CHG bathing and nasal mupirocin were used together in this study, it is not possible to determine whether the infection reduction was from CHG or mupirocin. This study adds to the growing literature identifying benefits of CHG bathing and nasal decolonization.

Daily CHG bathing in pediatric critical care unit patients has also been studied and resulted in a nonsignificant reduction in subsequent bacteremia.[67] CHG-impregnated cloths were used in all patients older than 2 months during the study period, and no adverse events were observed in this trial.

CHG is generally well tolerated, with a very low incidence of immediate adverse effects. Rarely, CHG may cause an allergic contact dermatitis

or local irritation. With the potential widespread adoption of CHG bathing in ICU settings, the question of CHG resistance is a concern.[68] Multidrug efflux pumps, encoded in plasmid-borne *qacA/B* genes, may lead to CHG resistance.[69] The issues of CHG resistance and the effects on the microbiome will need to be the focus of future studies as CHG bathing becomes a more common practice in health care settings.

Prophylaxis of Infection in Burn Wounds

The prevention of infection in the burned patient is extremely difficult because burn wound sites are favorable for bacterial overgrowth, the epidermal barrier is often defective for extended periods, and the patients are in the hospital, where multiple antibiotic-resistant organisms are found.[2] Frequent débridement and the establishment of an epidermis, or a surrogate such as a skin graft or skin substitute, are essential for the prevention of infection. As a result of the pathogenesis and pathophysiology of the burn wound, the delivery of systemic antimicrobial therapy to the deepest, most severely ischemic areas of the wound cannot be relied on because gradient diffusion from the wound periphery is the sole means of access.[70]

The use of topical antibacterial agents for burned patients is well established. Before the development of effective topical burn wound chemotherapy, burn wound sepsis was diagnosed as the principal cause of death in 60% of lethal burn injuries[71]; the use of mafenide acetate has reduced to 28% the incidence of burn wound sepsis as a cause of death. After administration, high antimicrobial concentrations are found on the wound surface, where the risk of bacterial contamination is the greatest. In patients with deep, extensive wounds, dense bacterial colonization, particularly by gram-positive cocci, often occurs within 24 hours; aerobic gram-negative bacilli typically appear within 3 to 7 days. If this initial bacterial colonization is not treated, deeper spread and ultimately systemic invasion of pathogenic bacteria can occur. Therefore, topical antibacterial therapy should be initiated as soon as possible to delay or prevent these processes.

There is evidence that effective topical antibacterial therapy delays colonization of the burn wound for a variable period (measured in days, not weeks), maintains the bacterial density of the wound at lower levels than those that could otherwise be achieved and for appreciable intervals (measured in weeks), and tends to result in a relatively homogeneous and less diverse wound flora than what would otherwise be expected.[70] The specific antimicrobial agent chosen for topical therapy should have a broad in vitro spectrum of activity against gram-positive cocci (staphylococci, streptococci, and enterococci) and the aerobic gram-negative microbiota (including *Pseudomonas aeruginosa*). Ideally, the agent should penetrate the eschar, but because it may be absorbed, it must have low toxicity[72]; the agent must also remain active in the presence of serum and necrotic debris. Furthermore, with the increasing use of cultured skin grafts in the therapeutic approach to the burned patient, topical antibacterials may be required to prevent microbial colonization and the destruction of grafts containing cultured skin cells. The successful use of topical agents prevents the bacterial conversion of superficial burns to deeper injury, results in the spontaneous healing of wounds that initially appeared clinically to be of full thickness, and decreases the frequency of episodes of systemic sepsis.[73] Specific topical agents for use in burned patients are discussed in Chapter 314.

Treatment of Pyoderma

There is no role for topical antibacterials in the treatment of erysipelas, cellulitis, or furuncles.

However, there is a role for topical agents in the management of one specific type of pyoderma—impetigo. Impetigo is a superficial infection of the skin caused by group A streptococci (see Chapter 197), *S. aureus,* or both. Bullous impetigo is usually caused by *S. aureus.* One of the goals of antimicrobial therapy in impetigo is to prevent the spread of infection to uninvolved skin.[2] Early uncontrolled and controlled trials of topical antibacterial therapy in patients with impetigo suggested the efficacy of topical antibacterials, although other studies found that systemic antimicrobial therapy was more efficacious.[70] Systemic antimicrobial therapy is somewhat superior to topical therapy in the management of streptococcal pyoderma, with swifter healing and fewer failures. However, topical therapy may be used early in infection, when the number of lesions is small and there is a reasonable chance that these agents will be scrupulously and skillfully applied.[74] Exclusions to the use of topical antibacterials in pyoderma include the following: bullous impetigo, because the pathogenesis of this exfoliative infection may lead to continuing infection, rapid spread, recurrence, or all of these, unless *S. aureus* is promptly eradicated; and extensive pyoderma, regardless of the clinical form or bacterial cause.[75] Topical mupirocin has been shown to be as efficacious as systemic antibiotics in the therapy for limited impetigo (see later).

Retapamulin, a newer topical antibacterial, has been approved for use in adults and children 9 months of age and older. Retapamulin administered twice daily for 5 days was compared with placebo or fusidic acid in two separate double-blind, randomized trials in patients with impetigo. The response rates for retapamulin were 85.6% versus 52.1% for placebo and 94.8% for retapamulin versus 90.1% for fusidic acid. Retapamulin was found to be superior to placebo and not inferior to fusidic acid. The two most commonly identified pathogens in these studies were *S. aureus* and *S. pyogenes*, with similar response rates against both organisms.

Topical antibacterial agents may have some efficacy in the therapy for secondary types of pyoderma, although the available studies generally did not include control groups.[74] Despite organism eradication, the underlying process persisted. Therefore a cure (in the sense of complete healing) was not achieved. Because topical antibacterials can lower the bacterial colony counts in acute dermatitis, the use of these agents in combination with topical glucocorticoids is a logical treatment regimen.[2]

Treatment of Erythrasma and Rosacea

Erythrasma is a cutaneous eruption caused by the bacterium *Corynebacterium minutissimum.* The rash of erythrasma is commonly found in intertriginous areas that include axillae, inframammary areas, the interspaces of toes, and intergluteal and crural folds. Once the diagnosis has been confirmed, systemic antibacterial therapy with erythromycin is usually prescribed as first-line therapy.[76] However, there is an important role for topical antibacterial therapy in the management of this dermatologic infection. Most experts recommend the addition of a topical agent to systemic therapy in patients with intertriginous area involvement and the exclusive use of topical therapy in those patients intolerant of the recommended active systemic therapies.[76] Topical 2% clindamycin has been shown to be effective in the treatment of erythrasma and, when it is in an alcohol-based formulation, has the additional advantage of a drying effect.[77] Topical fusidic acid has also been shown to be effective as a topical treatment for erythrasma, but is not available in the United States. Topically administered erythromycin, tetracycline, and chloramphenicol have all been evaluated and found not to be effective in the treatment of erythrasma.[76]

Rosacea is a dermatologic condition with several disease phases that include flushing, followed by erythrosis, papulopustular rosacea, and finally phimosis. The etiology of rosacea remains somewhat controversial and is considered to be multifactorial, depending on the phase of disease. *Helicobacter pylori* has been believed by some to be a potential causative factor, and the *Demodex* mite has been implicated as a significant contributing factor of papulopustular rosacea.[78] There are no clear data that rosacea has a bacterial etiology, although the disease clearly responds to both systemic and topical treatment with antibacterial agents. Metronidazole, in either a 1% cream or a 0.75% gel, is the topical therapy that has been most widely evaluated in the treatment of papulopustular rosacea and the preceding erythrosis. Numerous randomized controlled trials have confirmed the tolerability and superior efficacy of topical metronidazole.[79,80] Because topical metronidazole has no antiinflammatory effects, its mechanism of action with respect to a cure for rosacea remains unknown but is presumably antimicrobial. Topical clindamycin, retinoids, and azelaic acid in a 20% cream formulation have all also been identified as acceptable topical alternatives in the management of rosacea.[78]

Ivermectin is an antiparasitic agent that also targets overgrowth of *Demodex* mites and has antiinflammatory properties. Two randomized, double-blind, placebo-controlled trials have assessed the efficacy and safety of 1% topical ivermectin for papulopustular rosacea. At 12 weeks' follow-up both trials showed "clear" or "almost clear" on the Investigator

Global Assessment of Rosacea Severity Score (IGA-RSS) scale. No adverse effects were reported.[81]

Treatment of Acne Vulgaris

Topical antibacterials are helpful for inflammatory acne.[82,83] The proliferation of *Cutibacterium* (formerly *Propionibacterium*) *acnes* is considered critical for the development of inflammatory lesions. The blocked follicles become an ideal anaerobic culture medium filled with nutrients in the form of lipid substrates; *C. acnes* metabolizes the lipid, producing free fatty acids, and this may be a triggering mechanism that leads to retention hyperkeratosis and microcomedone formation. Benzoyl peroxide exerts its effects by bacteriostatic activity on the proliferation of *C. acnes.* Oxygen is liberated when the drug is decomposed by cysteine in the skin, and bacterial proteins are thus oxidized. After 2 weeks of daily application, a 10% benzoyl peroxide preparation reduces concentrations of free fatty acids by about 50% and *C. acnes* by about 98%, comparable to the levels obtained after 4 weeks of treatment with antibiotics.

Topical antibiotics are used almost universally by dermatologists for the treatment of acne vulgaris.[82,83] These agents also exert their beneficial effects by decreasing the population of *C. acnes* in the follicle, although not as effectively or rapidly as benzoyl peroxide, and they also inhibit the production of proinflammatory mediators by organisms that are not killed.[82] Preparations containing clindamycin and erythromycin are the most commonly used[82,83]; topical tetracyclines have also been used but are less effective than either clindamycin or erythromycin. Topical azelaic acid, a dicarboxylic acid derivative that is bacteriostatic for *C. acnes,* has been shown to reduce colony counts of *C. acnes* by about the same degree as clindamycin. However, the most effective topical antibacterial regimens against *C. acnes* are the combination formulations that include benzoyl peroxide and either erythromycin or clindamycin. A randomized 10-week trial comparing the efficacy of erythromycin (3%)–benzoyl peroxide (5%) gel with that of erythromycin (4%)–zinc (1.2%) solution in 72 acne vulgaris patients revealed that both inflammatory lesions and comedones showed a significantly greater percentage reduction from baseline in those patients receiving the erythromycin–benzoyl peroxide combination[84]; both physician and patient efficacy evaluations were also more favorable for this regimen. Additional studies have also demonstrated the efficacy of the combination formulation of benzoyl peroxide with erythromycin, and this regimen is considered one of the most effective in the treatment of acne. The combination formulation of 1% clindamycin and 5% benzoyl peroxide gel has been marketed and evaluated for its effectiveness in the treatment of acne vulgaris.[85] Several clinical trials have demonstrated that the twice-daily application of this product for 10 to 16 weeks was more effective in reducing the number of inflammatory lesions than 5% benzoyl peroxide, 1% clindamycin, or placebo gel in patients with mild to moderately severe acne.[86,87] In another multicenter blinded trial, clindamycin–benzoyl peroxide gel was directly compared with benzoyl peroxide alone and the erythromycin–benzoyl peroxide combination formulation.[88] The clindamycin–benzoyl peroxide was significantly more effective in reducing the mean number of inflammatory lesions than benzoyl peroxide alone, and it was similar in efficacy to erythromycin–benzoyl peroxide. Both patient and physician assessments at the end of the study indicated that global improvement was significantly greater with clindamycin–benzoyl peroxide than with benzoyl peroxide alone and similar to that identified with erythromycin–benzoyl peroxide. Therefore, the clindamycin–benzoyl peroxide and erythromycin–benzoyl peroxide formulations are equally efficacious and can both be considered first-line topical therapies in the treatment of acne vulgaris. Use of antibiotic-based preparations are typically for 3 months, but studies of long-term effects have not been performed. Dapsone 5% gel has also been studied and has been found to be particularly useful in inflammatory acne and in females.[89,90]

Elimination of *Staphylococcus aureus* Nasal Carriage

Decolonization to eliminate MRSA nasal carriage is a complex topic beyond the scope of this chapter. The general role of decolonization in the prevention of MRSA infections is unclear. Decolonization has been attempted in colonized hospital patients, in outpatients with recurrent MRSA infections, and as part of a universal decolonization protocol without assessment of MRSA carrier state. It has also been used in the prevention of dialysis catheter infections and in the prevention of SSIs, as discussed earlier. The optimal approach to MRSA decolonization for outpatients and inpatients is not known. Whether inpatient decolonization should be attempted only in the setting of outbreaks or more universally is also undecided. Currently, there is no definitive evidence to support routine MRSA decolonization of inpatients. However, decolonization may be reasonable in the setting of hospital outbreaks, for outpatients with recurrent MRSA infections, and within households where ongoing MRSA transmission is documented despite the implementation of other hygiene measures.[91,92,93]

With respect to decolonization in hospitalized patients, it is well known that 20% to 40% of healthy persons carry *S. aureus* in their anterior nares. In hospitalized patients, serious infection caused by *S. aureus* may occur from autoinoculation to susceptible sites or the transfer of organisms from another patient or staff member who is a carrier. Attempts to control hospital outbreaks have included methods to eradicate nasal carriage of staphylococci by means of systemic antimicrobial agents with or without topical treatment; however, recolonization is frequent, and the development of resistance has been reported.[94] Several topical antibacterial agents have been used in the nasal eradication of *S. aureus,* with varied degrees of success.

A systematic review of this subject was published by Ammerlaan and colleagues in 2009.[95] This review included all known studies investigating the eradication of *S. aureus* carriage. Of the 2388 studies identified, 23 met the authors' inclusion criteria, all of which were published between March 1977 and October 2008. Of these, 13 studies evaluated mupirocin, with either placebo or active comparator arms. In summary, short-term nasal application of mupirocin was shown to be effective at eradicating *S. aureus,* with an estimated 90% probability of success 1 week after treatment and approximately 60% after longer-term follow-up (ranging from 14 to 365 days). This compares with an estimated success rate from oral antibiotic administration of 60% 1 week after treatment and 50% after longer follow-up. The effectiveness of mupirocin was comparable among MSSA and MRSA carriers. Long-term duration of effect is not to be expected, and many patients will eventually recolonize. Decolonization using mupirocin has had variable efficacy in other groups, including a study of soldiers, in which no difference was found in MRSA infection rates when mupirocin was compared with placebo.[96]

Many experts recommend combination topical therapy with nasal mupirocin and CHG bathing, with or without oral antibiotics, when MRSA decolonization is desired.[92] A 5- to 10-day total course with the topical therapies is suggested. Longer courses should be avoided because of the potential for adverse effects and development of resistance. Once decolonization is complete, routine screening cultures are not recommended.[85] The value of repeated decolonization attempts is unknown.

A noteworthy concern associated with mupirocin decolonization is the development of acquired drug resistance. Based on the studies evaluated by Ammerlaan and colleagues,[95] the use of mupirocin is associated with a 1% risk of acquiring a drug-resistant strain during therapy. Although this is a low rate, recent surveillance studies have demonstrated mupirocin-resistant MRSA in up to 13% of the patients in institutions that do not practice routine mupirocin use and up to 65% in patients in areas where there is widespread use of mupirocin.[41]

SPECIFIC TOPICAL ANTIBACTERIALS

Numerous topical antibacterial agents are available for clinical use in various concentrations, vehicles, and mixtures (Table 38.3). Although they are used as topical agents, antimicrobials such as clindamycin, erythromycin, tetracycline, and gentamicin are covered in other chapters of this book. This section provides additional information on the four most common topical antimicrobials.

Bacitracin

Mechanism of Effects

Bacitracin is a polypeptide antibiotic produced by *Bacillus subtilis.* There are three bacitracin subgroups: A, B, and C. Subgroup A is the major constituent of commercial preparations.[97] Bacitracin contains a thiazoline ring and peptide side chains. After administration, it forms a complex

TABLE 38.3 Selected Topical Antibacterial Agents in Clinical Use

TOPICAL ANTIBACTERIAL (TRADE NAME)	CONCENTRATION	FREQUENCY	INDICATION
Azelaic acid (Azelex)	20% cream	Twice daily	Acne vulgaris
Benzoyl peroxide	2.5%–10%	Once to twice daily	Acne vulgaris
Clindamycin (Cleocin,[a] Clindagel)	1%, 2%	Twice daily	Acne vulgaris; bacterial vaginosis
Clindamycin–benzoyl peroxide (BenzaClin)	1%–5%	Twice daily	Acne vulgaris
Erythromycin (Emgel)	2%	Twice daily	Acne vulgaris
Erythromycin–benzoyl peroxide (Benzamycin)	3%–5%	Twice daily	Acne vulgaris
Fusidic acid (Fucidin)[b]	2%	Three times daily	Skin infections; eradication of nasopharyngeal carriage of *Staphylococcus aureus*
Mafenide (Sulfamylon)	—	Twice daily	Burns
Metronidazole (MetroGel, MetroCream, MetroLotion, Noritate)[c]	0.075%	Once to twice daily	Inflammatory pustules, papules, and rosacea; bacterial vaginosis
Mupirocin (Bactroban)	2% ointment	Three times daily	Skin infections; elimination of nasopharyngeal carriage of *S. aureus*
Polymyxin B–bacitracin–neomycin (Neosporin)[d]	5000 units/g–400 units/g–3.5 mg/g	One to three times daily	Prevention of infection in minor cuts, scrapes, and burns
Polymyxin B–neomycin–hydrocortisone (Cortisporin)	10,000 units/g–3.5 mg/g–0.5%	Two to four times daily	Corticosteroid-responsive dermatoses with secondary infection
Retapamulin (Altabax)	1% ointment	Two times daily for 5 days	Impetigo caused by *S. aureus* or *Streptococcus pyogenes*
Silver sulfadiazine (SSD, Silvadene)	1%	Once to twice daily	Burns

[a]The 2% formulation is recommended for bacterial vaginosis.
[b]Not licensed in the United States.
[c]Supplied in a 1% cream and given once daily for inflammatory lesions and erythema of rosacea.
[d]Maximum strength formulation contains 10,000 units/g polymyxin B, 500 units/g bacitracin, and 3.5 mg/g neomycin.

with C55-isoprenyl pyrophosphate, a component of the bacterial cell wall. This molecule acts as a carrier involved in the transfer of polysaccharides, peptidoglycans, and lipopolysaccharides to the growing cell wall. Therefore, formation of the bacterial cell wall is impaired.

In Vitro Spectrum of Activity

The activity of bacitracin is primarily against gram-positive organisms: staphylococci, streptococci, corynebacteria, and clostridia.[97] The development of resistance to bacitracin is rare, although it has been reported in *S. aureus*.

Clinical Uses

Topical bacitracin has been used for many years, although its efficacy in controlled clinical trials has never been shown. In impetigo, bacitracin ointment was shown to be 80% effective in clearing pathogenic organisms,[75] although slow or delayed healing was noted in one-third of those patients cured. Bacitracin was the least effective in bullous impetigo, in which four of six patients continued to develop new lesions, requiring systemic erythromycin therapy. Furthermore, in a trial comparing topical bacitracin with topical mupirocin or oral cephalexin for the treatment of impetigo, the treatment failed in most patients (six of nine) treated with bacitracin.[98] Bacitracin has also been evaluated in the eradication of nasal carriage of *S. aureus,* although its efficacy has never been shown.[99] For topical use, bacitracin is often formulated with neomycin, polymyxin B, or both (see Table 38.2).

Adverse Effects

Toxicity with bacitracin is minimal. Minor skin irritation may occur. Cases of anaphylaxis have been reported after the topical administration of bacitracin to open lesions[97]; these patients had previous multiple exposures to the drug. In addition, there have been rare reports of anaphylaxis after the use of bacitracin as an irrigating solution in the intraoperative setting and when used topically in conjunction with nasal packing after rhinoplasty.[100,101] Ready access to the systemic circulation appears to be a prerequisite for the development of anaphylaxis from this externally applied agent. On rare occasions, allergic contact dermatitis has been reported. Because bacitracin and polymyxin B are both derived from the *Bacillus* species, cross-reactivity between the two agents may occur.

Neomycin

Mechanism of Action

Neomycin is an aminoglycoside antibiotic isolated from cultures of *Streptomyces fradiae*.[97] The mechanism of action involves inhibition of protein synthesis by binding to the 30S subunit of the bacterial ribosome, leading to misreading of the genetic code; neomycin may also inhibit the bacterial DNA polymerase.

In Vitro Spectrum of Activity

Neomycin has in vitro activity against many gram-positive and gram-negative bacteria, including *Escherichia coli, Haemophilus influenzae, Proteus* species, *S. aureus,* and *Serratia* species. *P. aeruginosa* is generally resistant.[102] There is minimal in vitro activity against streptococci, although at the high concentrations achieved on the skin, *S. pyogenes* organisms are probably killed by topical neomycin preparations.[2] Resistance to neomycin has been reported in both gram-positive and gram-negative bacteria[74,97] and can be plasmid mediated; resistance to other aminoglycosides, such as kanamycin and gentamicin, may be present on the same plasmid.

Clinical Uses

Neomycin is widely used in combination with other antibiotics, antifungals, and corticosteroids because of its availability, relatively low cost, and perceived efficacy.[10,74] There are few well-controlled clinical trials documenting the efficacy and safety of topical neomycin.[75] Neomycin has been shown to enhance reepithelialization in wound healing.[11] However, in view of its well-documented contact sensitivity, possible systemic toxicity, and cross-reactivity with other antibiotics and because of the emergence of resistance, it is difficult to recommend the use of topical neomycin in the treatment of superficial skin infections.[97]

Adverse Effects

Neomycin is not absorbed through intact skin, although application to denuded or damaged epithelium can lead to sensitization and systemic

toxicity.[102] After systemic absorption, neomycin is excreted by the kidney. Patients with decreased renal function may develop ototoxicity, which is irreversible and may progress after discontinuation of the drug. Allergic contact sensitivity is widely reported, with a prevalence of 1% to 6% and an incidence of 3% to 6%.[102,103] The incidence of hypersensitivity, as assessed with patch testing in 390 patients with suspected contact dermatitis from topical medications, was approximately 36%.[104] Sensitivity is most likely to occur with chronic use on inflamed skin. Sensitivity to neomycin was reported in 49% of patients with a history of allergy to any topical agent.[97] Neomycin may also cause mast cell degranulation and histamine release.

Polymyxin B

Mechanism of Action

Polymyxin B is isolated from the aerobic gram-positive rod *Bacillus polymyxa,* a soil organism (see Chapter 32). The polymyxins are cationic, branched, cyclic decapeptides that destroy bacterial membranes with a surface detergent–like mechanism by interacting with membrane phospholipids and increasing cellular permeability.

In Vitro Spectrum of Activity

The spectrum of activity of polymyxin B is almost exclusively limited to gram-negative organisms. The agent is bactericidal against many aerobic gram-negative organisms, including *P. aeruginosa,* but it is not active against *Proteus* species and is poorly active against *Providencia, Burkholderia,* and *Serratia* species. There is no in vitro activity against gram-positive organisms. Although *Pseudomonas* is usually sensitive, the in vitro activity of polymyxin B against *Pseudomonas* is promptly neutralized by divalent cations at concentrations in body fluids. Organisms resistant to polymyxin B have cell walls that prevent access of the drug to the bacterial cell membrane. There is no cross-resistance with other antimicrobial agents, and resistance rarely develops during therapy.

Clinical Uses

Polymyxin B is used primarily in the prevention and treatment of minor skin infections. It is most often added to neomycin and bacitracin (see earlier) to broaden coverage against gram-negative organisms.

Adverse Effects

Because polymyxin B binds to cell membranes with very high affinity, there is little systemic absorption, and there are few reactions even when applied to open wounds. Contact sensitization has been reported.

Mupirocin

Structure and Mechanism of Action

Mupirocin has a chemical structure unlike that of any other antimicrobial agent,[105,106] containing a short fatty acid side chain (9-hydroxy-nonanoic acid) linked to monic acid by an ester linkage. Mupirocin is formulated in a bland water-miscible ointment base consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin used to be called pseudomonic acid because its major metabolite is derived from submerged fermentation by *Pseudomonas fluorescens*. Pseudomonic acid A represents 90% to 95% of the pseudomonic acid family and is responsible for most of the antibacterial activity; three other minor metabolites of similar chemical structure and antimicrobial spectrum have been denoted as pseudomonic acids B, C, and D.[98] Mupirocin inhibits bacterial RNA and protein synthesis by binding to bacterial isoleucyl–transfer RNA (tRNA) synthetase, which catalyzes the formation of isoleucyl-tRNA from isoleucine and tRNA.[105,106] This prevents the incorporation of isoleucine into protein chains of the bacterial cell wall, leading to the arrest of protein synthesis. Because of its unique structure and unique mechanism of action, mupirocin does not cross react with other antimicrobial agents.

In Vitro Spectrum of Activity

Mupirocin is bacteriostatic at low concentrations near the minimal inhibitory concentration (MIC) for *S. aureus,* but it is bactericidal at concentrations achieved by topical administration (20,000 µg/mL with the 2% formulation) after 24 to 36 hours of exposure.[105] It is highly active in vitro against MRSA, staphylococcal strains resistant to other antibacterials (e.g., penicillin, streptomycin, neomycin, erythromycin, fusidic acid, lincomycin, chloramphenicol, and tetracycline), and streptococci that are associated with primary and secondary skin infections.[105] The exception to the antistreptococcal activity of mupirocin is the enterococci. Mupirocin is inactive in vitro against *P. aeruginosa,* anaerobes, fungi, and the Enterobacteriaceae. An important feature of the antibacterial spectrum of mupirocin is its weaker in vitro activity against the normal skin flora (e.g., *Micrococcus, Corynebacterium,* and *Propionibacterium*), which is part of the skin's natural defense against infection. The in vitro antibacterial activity of mupirocin is the greatest at an acidic pH, which is advantageous because of the low pH of the skin; in one study, mupirocin was fourfold to eightfold more active in vitro at pH 6 than at pH 7.

Long-term therapy with mupirocin can lead to the development of resistant staphylococci,[105,107] an effect that is irreversible. Staphylococcal isolates with low- or intermediate-level resistance have MICs in the range of 8 to 256 µg/mL, whereas isolates with MICs at or greater than 512 µg/mL demonstrate high-level resistance. This resistance can be induced in *S. aureus* by subculturing the organisms onto media containing increasing concentrations of the drug. Naturally occurring clones of staphylococci with low-level resistance to mupirocin have been described, although their clinical significance is unclear because the concentration of mupirocin in ointment exceeds 20,000 µg/mL. High-level mupirocin resistance, associated with clinical treatment failure, has emerged in both MRSA and *Staphylococcus epidermidis.*[108] Most mupirocin-resistant staphylococcal isolates have been found in patients with chronic skin infections, many of whom had been treated with prolonged courses of mupirocin.[106] Researchers from France reported that a 5-day course of intranasal mupirocin for decolonization of a patient with glycopeptide-intermediate *S. aureus* (GISA) failed to eradicate this isolate, even though the strain was susceptible in vitro to mupirocin.[109] The patient went on to develop nosocomial pneumonia with the GISA strain, and the strain had developed resistance to mupirocin at repeat testing. Several mechanisms have been advanced to explain mupirocin resistance in staphylococci. Low-level resistance is most likely mediated by altered access to binding sites on isoleucyl-tRNA synthetase, whereas high-level resistance appears to be mediated by a transferable plasmid carrying the *mupA* gene, which encodes a modified isoleucyl-tRNA synthetase.[106] It has been suggested that high-level resistance may have evolved by the conjugate transfer of plasmids from enterococci,[110] which are inherently resistant to mupirocin; the conjugate transfer of high-level mupirocin resistance has also been observed among coagulase-negative staphylococci.[111] A study has demonstrated that two different isoleucyl-tRNA synthetase enzymes are present in highly mupirocin-resistant *S. aureus* isolates (MIC ≥512 µg/mL), whereas only a chromosomally encoded isoleucyl-tRNA synthetase enzyme was detected in strains expressing intermediate levels of resistance (MIC 8 to 256 µg/mL). Commercially available Etests (bioMérieux, Durham, NC) to detect mupirocin resistance in *S. aureus* are available and are quite accurate in differentiating low-level from high-level resistance patterns.[112] Etests compare favorably with the more traditional disk diffusion method and MIC determination in the detection of resistance.[113] Adding to the concerns about mupirocin resistance is the identification of the gene encoding high-level mupirocin resistance in USA300 MRSA clones, one of the most common clones found in community-acquired MRSA infections.

Pharmacokinetics

After systemic administration, mupirocin is immediately metabolized to monic acid, which is bacteriologically inactive and rapidly eliminated (plasma half-life, <30 minutes). Mupirocin is not appreciably absorbed after topical administration to intact skin. In one study, a mean of 0.24% of applied radiolabeled ointment was absorbed through intact skin after 24 hours of occlusion.[107] Greater penetration of mupirocin is expected in damaged or diseased skin. However, any drug that is absorbed is converted to monic acid, formed by deesterification of mupirocin at the ester linkage between the side chain and the nucleus, and rapidly eliminated in the urine.[90] Skin can also metabolize mupirocin to its inactive metabolite but at a rate less than 3%. Therefore, because only small amounts of mupirocin penetrate the skin and equally small amounts are degraded, most of the drug is available to act at the skin level.

Because mupirocin is highly protein bound (approximately 95%), its activity decreases in the presence of serum.[98]

Clinical Uses

Mupirocin is used primarily in skin infections, such as impetigo and folliculitis, which are usually caused by *S. aureus* and *S. pyogenes,* to decolonize the nares in outbreak settings and as prophylaxis against a variety of catheter-related infections and SSIs. In trials of mupirocin alone in the therapy for impetigo (772 evaluated patients),[114–116] clinical cure rates ranged from 81% to 100% and bacterial elimination rates from 67% to 100%. Several trials have shown mupirocin to be more effective in the treatment of impetigo than its polyethylene glycol vehicle, which also has antibacterial activity. Clinical cure and bacterial elimination rates have ranged from 85% to 100% and from 80% to 95%, respectively, for mupirocin versus from 12% to 84% and from 12% to 63%, respectively, for the vehicle.[114–117] Of eight comparative trials of mupirocin versus several other topical antibacterials (neomycin, fusidic acid, chlortetracycline, polymyxin B–bacitracin–neomycin),[114,118,119] six found mupirocin to be the most effective agent. Multiple studies have also compared topical mupirocin with systemic antibiotics (erythromycin, cloxacillin, dicloxacillin, flucloxacillin, ampicillin, and cephalexin) in the therapy for impetigo, and topical mupirocin was found to be as or more effective than the oral agent.[98,114] However, in many of these studies, the entry criteria excluded patients who, in the judgment of the investigator, had too many lesions to allow reliable compliance with topical therapy. No studies have shown that topical therapy is as effective as systemic antimicrobial therapy for the treatment of widespread, extensive lesions.

Mupirocin is effective for the treatment of secondarily infected eczema, burns, lacerations, and leg ulcers. In a study in which 33 centers contributed a total of 1030 cases,[120] mupirocin ointment produced significantly better bacteriologic and clinical responses than its vehicle in the treatment of secondary skin infections. Of 851 evaluated patients with 1131 pathogens, mupirocin eliminated 87% (505/583) of pathogens versus only 53% (288/548) for the vehicle. In a double-blind, vehicle-controlled study, mupirocin successfully eradicated 85% of *S. aureus* in 33 patients, compared with a 6% eradication rate in the vehicle-treated group[121] for all pathogens; the success rate of mupirocin versus the vehicle was 69% versus 14%, respectively. Comparative trials have also demonstrated the efficacy of mupirocin compared with other topical antibacterials and systemic antimicrobial agents in the treatment of secondary skin infections.

The use of mupirocin to eliminate nasal carriage of *S. aureus* in a variety of settings that include outbreaks, preoperative patients, and chronic dialysis patients is discussed earlier in this chapter.

Adverse Effects

Mupirocin is not associated with substantial toxicity in humans because of its very low affinity for mammalian isoleucyl-tRNA synthetase. The propylene glycol base may irritate mucous membranes and eroded skin. There is minimal potential for inducing allergic contact dermatitis; only two cases have been reported.[122] The drug is not phototoxic. Local effects, such as itching, stinging, or rash, have been reported when mupirocin is used on broken skin or mucous membranes. Chronic exposure to topical mupirocin rarely has been associated with the rupture of polyurethane peritoneal dialysis catheters, which may be caused by the vehicle portion of the preparation interacting with the polyurethane in the catheter.[123] No photosensitivity reactions have occurred. Mupirocin is listed as a pregnancy category B drug. In experimental animal models, doses were used that were between 14 and 43 times greater than usual human doses, and no teratogenic effects, embryotoxicity, or fertility or reproductive issues were identified.[120] Prolonged use may lead to the overgrowth of nonsusceptible organisms such as fungi.

Key References

The complete reference list is available online at Expert Consult.

4. Hill RLR, Casewell MW. The in-vitro activity of povidone-iodine cream against *Staphylococcus aureus* and its bioavailability in nasal secretions. *J Hosp Infect*. 2000;45:198–205.
5. Centers for Disease Control and Prevention. Guideline for hand hygiene in health-care settings. *MMWR Morb Morbid Wkly Rep*. 2002;52:1–44.
7. O'Grady NP, Alexander M, Burns LA, et al Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections; 2011. http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf.
12. Eaglstein WH, Mertz P, Alvarez OM. Effect of topically applied agents on healing wounds. *Clin Dermatol*. 1984;2:112–115.
20. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *N Engl J Med*. 2002;346:1871–1877.
27. Darouiche RO, Wall MJ, Itani KMF, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical site antisepsis. *N Engl J Med*. 2010;362:18–26.
28. Noorani A, Rabey N, Walsh SR, et al. Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. *Br J Surg*. 2010;97:1614–1620.
29. Lee I, Agarwal RK, Lee BY, et al. Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol*. 2010;31:1219–1229.
30. Swenson BR, Hedrick TL, Metzger R, et al. Effects of preoperative skin preparation on postoperative wound infection rates: a prospective study of 3 skin preparation protocols. *Infect Control Hosp Epidemiol*. 2009;30:964–971.
32. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database Syst Rev*. 2007;(2):CD004985.
33. Ho KM, Litton E. Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. *J Antimicrob Chemother*. 2006;58:281–287.
34. Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA*. 2009;301:1118–1123.
37. Levin A, Mason AJ, Jindal KK, et al. Prevention of hemodialysis subclavian vein catheter infections by topical povidone-iodine. *Kidney Int*. 1991;40:934–938.
40. Herwaldt LA. Reduction of *Staphylococcus aureus* nasal carriage and infection in dialysis patients. *J Hosp Infect*. 1998;40:513–523.
48. Thodis E, Passadakis P, Panagoutsos S, et al. The effectiveness of mupirocin preventing *Staphylococcus aureus* in catheter-related infections in peritoneal dialysis. *Adv Perit Dial*. 2000;16:257–261.
53. Patel PR, Yi SH, Booth S, et al. Bloodstream infection rates in outpatient hemodialysis facilities participating in a collaborative prevention effort: a quality improvement report. *Am J Kidney Dis*. 2013;62:322–330.
54. Johnson DW, MacGinley R, Kay TD, et al. A randomized trial of topical exit site mupirocin application in patients with tunneled, cuffed, haemodialysis catheters. *Nephrol Dial Transplant*. 2002;17:1802–1807.
55. McCann M, Moore ZE. Interventions for preventing infectious complications in haemodialysis patients with central venous catheters. *Cochrane Database Syst Rev*. 2010;(1):CD006894.
61. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302:2323–2329.
62. Climo MW, Yokoe DS, Warren DK, et al. Effect of chlorhexidine bathing on hospital-acquired infection. *N Engl J Med*. 2013;368:533–542.
63. O'Horo JC, Germana L, Silva M, et al. The efficacy of daily bathing with chlorhexidine for reducing healthcare-associated bloodstream infections: meta-analysis. *Infect Control Hosp Epidemiol*. 2012;33:257–267.
64. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. 2013;368:2255–2265.
65. Climo MW, Sepkowitz KA, Zuccotti G, et al. The efficacy of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococcus, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. *Crit Care Med*. 2009;37:1858–1865.
67. Milstone AM, Elward A, Song X, et al. Daily chlorhexidine bathing to reduce bactaeremia in critically ill children: a multicentre, cluster-randomized, crossover trial. *Lancet*. 2013;381:1099–1106.
68. Vali L, Davies SE, Lai LL, et al. Frequency of biocide resistance genes, antibiotic resistance and the effect of chlorhexidine exposure on clinical methicillin-resistant *Staphylococcus aureus* isolates. *J Antimicrob Chemother*. 2008;61:524–532.
69. Longtin J, Seah C, Siebert K. Distribution of antiseptic resistance genes *qacA*, *qacb* and *smr* in methicillin-resistant *Staphylococcus aureus* isolated in Toronto, Canada from 2005-2009. *Antimicrob Agents Chemother*. 2011;55:2999–3001.
72. Andreassi L, Flori L. Pharmacologic treatment of burns. *Clin Dermatol*. 1992;9:453–458.
75. Dillon HC Jr. Topical and systemic therapy for pyodermas. *Int J Dermatol*. 1980;19:443–451.
85. Warner GT, Plosker GL. Clindamycin/benzoyl peroxide gel. *Am J Clin Dermatol*. 2002;3:349–360.
91. van Rijen M, Bonten M, Wenzel R, et al. Mupirocin ointment for preventing *Staphylococcus aureus* infections in nasal carriers. *Cochrane Database Syst Rev*. 2008;(4):CD006216.
92. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
94. Lee AS, Macedo-Vinas M, Francois P, et al. Impact of combined low-level mupirocin and genotypic chlorhexidine resistance on persistent methicillin-resistant *Staphylococcus aureus* nasal carriage after decolonization therapy: a case-control study. *Clin Infect Dis*. 2011;52:1422–1430.
95. Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis*. 2009;48:922–930.
100. Blas M, Briesacher KS, Lobato E. Bacitracin irrigation: a cause of anaphylaxis in the operating room. *Anesth Analg*. 2000;91:1027–1028.
123. Riu S, Ruiz C, Martinez-Vea C, et al. Spontaneous rupture of polyurethane peritoneal catheter: a possible deleterious effect of mupirocin ointment. *Nephrol Dial Transplant*. 1998;13:1870–1871.

References

1. Russell AD. Plasmids and bacterial resistance to biocides. *J Appl Microbiol*. 1997;83:155–165.
2. Feingold DS, et al. Antibacterial agents. In: Fitzpatrick TB, Eisen AZ, Wolff K, eds. *Dermatology in General Medicine*. 3rd ed. New York: McGraw-Hill; 1987:2550–2552.
3. Kaye ET, Kaye KM. Topical antibacterial agents. *Infect Dis Clin North Am*. 1995;9:547–559.
4. Hill RLR, Casewell MW. The in-vitro activity of povidone-iodine cream against *Staphylococcus aureus* and its bioavailability in nasal secretions. *J Hosp Infect*. 2000;45:198–205.
5. Centers for Disease Control and Prevention. Guideline for hand hygiene in health-care settings. *MMWR Morb Morbid Wkly Rep*. 2002;52:1–44.
6. Maki DG, Ringer M, Alvarado CJ. Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet*. 1991;338:339–343.
7. O'Grady NP, Alexander M, Burns LA, et al. Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections; 2011. http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf.
8. Suller MTE, Russell AD. Triclosan and antibiotic resistance in *Staphylococcus aureus*. *J Antimicrob Chemother*. 2000;46:11–18.
9. Yazdankhah SP, Scheie AA, Hoiby EA, et al. Triclosan and antimicrobial resistance in bacteria: an overview. *Microb Drug Resist*. 2006;12:83–88.
10. US Food and Drug Administration. FDA issues final rule on safety and effectiveness of antibacterial soaps; September 2, 2016. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm517478.htm. Accessed September 14, 2018.
11. Leyden JJ, Sulzberger MB. Topical antibiotics and minor skin trauma. *Am Fam Physician*. 1981;23:121–125.
12. Eaglstein WH, Mertz P, Alvarez OM. Effect of topically applied agents on healing wounds. *Clin Dermatol*. 1984;2:112–115.
13. Maddox JS, Ware JC, Dillon HC Jr. The natural history of streptococcal skin infection: prevention with topical antibiotics. *J Am Acad Dermatol*. 1985;13:207–212.
14. Eaglstein WH, Falanga V. Chronic wounds. *Surg Clin North Am*. 1997;77:689–700.
15. Filius PM, Gyssens IC. Impact of increasing antimicrobial resistance on wound management. *Am J Clin Dermatol*. 2002;3:1–7.
16. O'Meara S, Al-Kurdi D, Ologun Y, et al. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev*. 2014;(1):CD003557.
17. Qaseem A, Humphrey L, Forciea M, et al. Treatment of pressure ulcers: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2015;162:370–379.
18. Raz R, Miron D, Colodner R, et al. A 1-year trial of nasal mupirocin in the prevention of recurrent staphylococcal nasal colonization and skin infection. *Arch Intern Med*. 1996;156:1109–1112.
19. Fritz S, Camins B, Eisenstein K, et al. Effectiveness of measures to eradicate *Staphylococcus aureus* carriage in patients with community associated skin and soft tissue infections: a randomized control trial. *Infect Control Hosp Epidemiol*. 2011;32:872–880.
20. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *N Engl J Med*. 2002;346:1871–1877.
21. Farr BM. Mupirocin to prevent *S. aureus* infections [editorial]. *N Engl J Med*. 2002;346:1905–1906.
22. Saraswat MK, Magruder JT, Crawford TC, et al. Preoperative *Staphylococcus aureus* screening and targeted decolonization in cardiac surgery. *Ann Thorac Surg*. 2017;104:1349–1356. ;.
23. Schweizer ML, Chiang HY, Septimus E, et al. Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery. *JAMA*. 2015;313:2162–2171. Jun 2.
24. Schweizer M, Perencevich E, McDaniel J, et al. Effectiveness of a bundled intervention of decolonization and prophylaxis to decrease gram positive surgical site infections after cardiac and orthopedic surgery: systematic review and meta-analysis. *BMJ*. 2013;f2743.
25. Bebko SP, Green DM, Awad SS. Effect of a preoperative decontamination protocol on surgical site infections in patients undergoing elective orthopedic surgery with hardware implantation. *JAMA Surg*. 2015;150:390–395. May.
26. Phillips M, Rosenberg A, Shopsin B, et al. Preventing surgical site infections: a randomized, open-label trial of nasal mupirocin ointment and nasal povidone-iodine solution. *Infect Control Hosp Epidemiol*. 2014;35:826–832. Jul.
27. Darouiche RO, Wall MJ, Itani KMF, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical site antisepsis. *N Engl J Med*. 2010;362:18–26.
28. Noorani A, Rabey N, Walsh SR, et al. Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. *Br J Surg*. 2010;97:1614–1620.
29. Lee I, Agarwal RK, Lee BY, et al. Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol*. 2010;31:1219–1229.
30. Swenson BR, Hedrick TL, Metzger R, et al. Effects of preoperative skin preparation on postoperative wound infection rates: a prospective study of 3 skin preparation protocols. *Infect Control Hosp Epidemiol*. 2009;30:964–971.
31. Broach RB, Paulson EC, Scott C, et al. Randomized controlled trial of two alcohol-based preparations for surgical site antisepsis in colorectal surgery. *Ann Surg*. 2017;266:946–951. Dec.
32. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database Syst Rev*. 2007;(2):CD004985.
33. Ho KM, Litton E. Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. *J Antimicrob Chemother*. 2006;58:281–287.
34. Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA*. 2009;301:1118–1123.
35. Timsit J, Mimoz O, Mourvillier B, et al. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing Catheter-related infections in critically ill adults. *Am J Respir Crit Care Med*. 2012;186:1272–1278.
36. Maki DG, Band JD. A comparative study of polyantibiotic and iodophor ointments in prevention of vascular catheter-related infection. *Am J Med*. 1981;70:739–744.
37. Levin A, Mason AJ, Jindal KK, et al. Prevention of hemodialysis subclavian vein catheter infections by topical povidone-iodine. *Kidney Int*. 1991;40:934–938.
38. Gokal R. Peritoneal dialysis: prevention and control of infection. *Drugs Aging*. 2000;17:269–282.
39. Piraino B, Perlmutter JA, Holley JL, et al. *Staphylococcus aureus* peritonitis is associated with *Staphylococcus aureus* nasal carriage in peritoneal dialysis patients. *Perit Dial Int*. 1992;13:5332–5334.
40. Herwaldt LA. Reduction of *Staphylococcus aureus* nasal carriage and infection in dialysis patients. *J Hosp Infect*. 1998;40:513–523.
41. Wilson AP, Lewis C, O'Sullivan A, et al. The use of povidone-iodine in exit site care for patients undergoing CAPD. *J Hosp Infect*. 1997;35:287–293.
42. Bending M, Mellotte G, Hashmi C, et al. Nasal mupirocin prevents *S. aureus* exit site infection during peritoneal dialysis. *J Am Soc Nephrol*. 1996;7:2403–2408.
43. Pérez-Fontán M, García-Falcón T, Rosales M, et al. Treatment of *Staphylococcus aureus* nasal carriage in continuous ambulatory peritoneal dialysis (CAPD) with mupirocin: long-term results. *Am J Kidney Dis*. 1993;22:700–712.
44. Thodis E, Passadakis P, Vargemezis V, et al. Prevention of catheter-related infections in patients on CAPD. *Int J Artif Organs*. 2001;24:671–682.
45. Mupirocin Study Group. Nasal mupirocin prevents *Staphylococcus aureus* exit-site infections during peritoneal dialysis. *J Am Soc Nephrol*. 1996;7:2403–2408.
46. Davey P, Craig AM, Hau C, et al. Cost-effectiveness of prophylactic nasal mupirocin in patients undergoing peritoneal dialysis based on a randomized, placebo-controlled trial. *J Antimicrob Chemother*. 1999;43:105–112.
47. Bernardini J, Piraino B, Holley J, et al. A randomized trial of *Staphylococcus aureus* prophylaxis in peritoneal dialysis patients: mupirocin calcium ointment 2% applied to the exit site versus cyclic oral rifampin. *Am J Kidney Dis*. 1996;27:695–700.
48. Thodis E, Passadakis P, Panagoutsos S, et al. The effectiveness of mupirocin preventing *Staphylococcus aureus* in catheter-related infections in peritoneal dialysis. *Adv Perit Dial*. 2000;16:257–261.
49. Thodis E, Bhaskaran S, Passadakis P, et al. Decrease in *Staphylococcus aureus* exit-site infections and peritonitis in CAPD patients by local application of mupirocin ointment at the catheter exit site. *Perit Dial Int*. 1998;18:261–270.
50. Casey M, Taylor J, Clinard P, et al. Application of mupirocin cream at the catheter exit site reduces exit-site infections and peritonitis in peritoneal dialysis patients. *Perit Dial Int*. 2000;20:566–574.
51. Tsai CC, Yang PS, Liu CL, et al. Comparison of topical mupirocin and gentamicin in the prevention of peritoneal dialysis-related infections: A systematic review and meta-analysis. *Am J Surg*. 2018;215:179–185.
52. Liakopoulos V, Nikitidou O, Kalathas T, et al. Peritoneal dialysis-related infections recommendations: 2016 update. What is new? *Int Urol Nephrol*. 2017;49:2177–2184.
53. Patel PR, Yi SH, Booth S, et al. Bloodstream infection rates in outpatient hemodialysis facilities participating in a collaborative prevention effort: a quality improvement report. *Am J Kidney Dis*. 2013;62:322–330.
54. Johnson DW, MacGinley R, Kay TD, et al. A randomized trial of topical exit site mupirocin application in patients with tunneled, cuffed, haemodialysis catheters. *Nephrol Dial Transplant*. 2002;17:1802–1807.
55. McCann M, Moore ZE. Interventions for preventing infectious complications in haemodialysis patients with central venous catheters. *Cochrane Database Syst Rev*. 2010;(1):CD006894.
56. Fong IW. Prevention of haemodialysis and peritoneal dialysis catheter-related infection by topical povidone-iodine. *Postgrad Med J*. 1993;69:515–517.
57. Boelaert JR, de Smedt RA, de Bacre YA, et al. The influence of calcium mupirocin nasal ointment on the incidence of *Staphylococcus aureus* infections in haemodialysis patients. *Nephrol Dial Transplant*. 1989;4:278–281.
58. Boelaert JR, van Landuyt HW, Godard CA, et al. Nasal mupirocin ointment decreases the incidence of *Staphylococcus aureus* bacteremias in haemodialysis patients. *Nephrol Dial Transplant*. 1993;8:235–239.
59. Kluytmans JA, Manders MJ, van Bommel E, et al. Elimination of nasal carriage of *Staphylococcus aureus* in hemodialysis patients. *Infect Control Hosp Epidemiol*. 1996;17:793–797.
60. Bloom BS, Fendrick AM, Chernew ME, et al. Clinical and economic effects of mupirocin calcium in preventing *Staphylococcus aureus* infection in hemodialysis patients: a decision analysis. *Am J Kidney Dis*. 1996;27:687–694.
61. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302:2323–2329.
62. Climo MW, Yokoe DS, Warren DK, et al. Effect of chlorhexidine bathing on hospital-acquired infection. *N Engl J Med*. 2013;368:533–542.
63. O'Horo JC, Germana L, Silva M, et al. The efficacy of daily bathing with chlorhexidine for reducing healthcare-associated bloodstream infections: meta-analysis. *Infect Control Hosp Epidemiol*. 2012;33:257–267.
64. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. 2013;368:2255–2265.
65. Climo MW, Sepkowitz KA, Zuccotti G, et al. The efficacy of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus,* and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. *Crit Care Med*. 2009;37:1858–1865.
66. Noto MJ, Domenico HJ, Byrne DW, et al. Chlorhexidine bathing and health care-associated infections: a randomized clinical trial. *JAMA*. 2015;313:369–378.
67. Milstone AM, Elward A, Song X, et al. Daily chlorhexidine bathing to reduce bactaeremia in critically ill children: a multicentre, cluster-randomized, crossover trial. *Lancet*. 2013;381:1099–1106.
68. Vali L, Davies SE, Lai LL, et al. Frequency of biocide resistance genes, antibiotic resistance and the effect of chlorhexidine exposure on clinical methicillin-resistant *Staphylococcus aureus* isolates. *J Antimicrob Chemother*. 2008;61:524–532.
69. Longtin J, Seah C, Siebert K. Distribution of antiseptic resistance genes *qacA, qacB* and *smr* in methicillin-resistant *Staphylococcus aureus* isolated in Toronto, Canada from 2005-2009. *Antimicrob Agents Chemother*. 2011;55:2999–3001.
70. Monafo WW, Freedman B. Topical therapy for burns. *Surg Clin North Am*. 1987;67:133–145.
71. Pruitt BA Jr, McManus AT, Kim SH, et al. Burn wound infections: current status. *World J Surg*. 1998;22:135–145.
72. Andreassi L, Flori L. Pharmacologic treatment of burns. *Clin Dermatol*. 1992;9:453–458.
73. Cimochowski GE, Harostock MD, Brown R, et al. Intranasal mupirocin reduces sternal wound infection after open heart surgery in diabetics and nondiabetics. *Ann Thorac Surg*. 2001;71:1572–1579.
74. Leyden JJ, Kligman AM. Rationale for topical antibiotics. *Cutis*. 1978;22:515–528.
75. Dillon HC Jr. Topical and systemic therapy for pyodermas. *Int J Dermatol*. 1980;19:443–451.

76. Holdiness MR. Management of cutaneous erythrasma. *Drugs*. 2002;62:1131–1141.
77. Cochran RJ, Rosen D, Landers T. Topical treatment for erythrasma. *Int J Dermatol*. 1981;20:562–564.
78. Rebora A. The management of rosacea. *Am J Clin Dermatol*. 2002;3:489–496.
79. Breneman D, Stewart D, Hevia O, et al. A double blind multicenter clinical trial comparing efficacy of once daily metronidazole 1% cream to vehicle in patients with rosacea. *Cutis*. 1998;61:44–47.
80. Jorizzo J, Lebwohl M, Tobey R. The efficacy of metronidazole 1% cream once daily compared with metronidazole cream 1% twice daily and their vehicles in rosacea: a double-blind clinical trial. *J Am Acad Dermatol*. 1998;395:502–504.
81. Stein L, Kircik L, Fowler J, et al. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol*. 2014;13:316–323. Mar.
82. Leyden JJ. Therapy for acne vulgaris. *N Engl J Med*. 1997;336:1156–1162.
83. Weiss JS. Current options for the topical treatment of acne vulgaris. *Pediatr Dermatol*. 1997;14:480–488.
84. Chu A, Huber FJ, Plott RT. The comparative efficacy of benzoyl peroxide 5%/erythromycin 3% gel and erythromycin 4%/zinc 1.2% solution in the treatment of acne vulgaris. *Br J Dermatol*. 1997;136:235–238.
85. Warner GT, Plosker GL. Clindamycin/benzoyl peroxide gel. *Am J Clin Dermatol*. 2002;3:349–360.
86. Lookingbill DT, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *J Am Acad Dermatol*. 1997;4:590–595.
87. Tschen EH, Katz HI, Jones TM, et al. A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. *Cutis*. 2001;67:165–169.
88. Leyden JJ, Hickman JG, Jarratt MT, et al. The efficacy and safety of a combination benzoyl peroxide/clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination product. *J Cutan Med Surg*. 2001;5:37–42.
89. Lucky AW, Maloney JM, Robert J, et al. Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long term (1 year) treatment. *J Drugs Dermatol*. 2007;6:981.
90. Tanghetti E, Harper JC, Oefelein MG. The efficacy and tolerability of dapsone 5% gel in female vs male patients with facial acne vulgaris: gender as a clinically relevant outcome variable. *J Drugs Dermatol*. 2012;11:1417.
91. van Rijen M, Bonten M, Wenzel R, et al. Mupirocin ointment for preventing *Staphylococcus aureus* infections in nasal carriers. *Cochrane Database Syst Rev*. 2008;(4):CD006216.
92. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
93. Buehlmann M, Frei R, Fener L, et al. Highly effective regimen for decolonization of methicillin-resistant *Staphylococcus aureus* carriers. *Infect Control Hosp Epidemiol*. 2008;29:510–516.
94. Lee AS, Macedo-Vinas M, Francois P, et al. Impact of combined low-level mupirocin and genotypic chlorhexidine resistance on persistent methicillin-resistant *Staphylococcus aureus* nasal carriage after decolonization therapy: a case-control study. *Clin Infect Dis*. 2011;52:1422–1430.
95. Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis*. 2009;48:922–930.
96. Ellis MW, Griffith ME, Dooley DP, et al. Targeted intranasal mupirocin to prevent colonization and infection by community-associated methicillin-resistant *Staphylococcus aureus* strains in soldiers: a cluster randomized controlled trial. *Antimicrob Agents Chemother*. 2007;51:3591–3596.
97. Winkelman W, Gratton D. Topical antibacterials. *Clin Dermatol*. 1989;7:156–162.
98. Bass JW, Chan DS, Creamer KM, et al. Comparison of oral cephalexin, topical mupirocin and topical bacitracin for treatment of impetigo. *Pediatr Infect Dis J*. 1997;16:708–710.
99. Yu VL, Goetz A, Wagener M, et al. *Staphylococcus aureus* nasal carriage and infection in patients on hemodialysis: efficacy of antibiotic prophylaxis. *N Engl J Med*. 1986;315:91–96.
100. Blas M, Briesacher KS, Lobato E. Bacitracin irrigation: a cause of anaphylaxis in the operating room. *Anesth Analg*. 2000;91:1027–1028.
101. Gall R, Blakley B, Warrington R, et al. Intraoperative anaphylactic shock from bacitracin nasal packing after septorhinoplasty. *Anesthesiology*. 1999;91:1545–1547.
102. MacDonald RH, Beck M. Neomycin: a review with particular reference to dermatological usage. *Clin Exp Dermatol*. 1983;8:249–258.
103. Gette MT, Marks JG Jr, Maloney ME. Frequency of postoperative allergic contact dermatitis to topical antibiotics. *Arch Dermatol*. 1992;128:365–367.
104. Bajaj AK, Gupta SC. Contact hypersensitivity to topical antibacterial agents. *Int J Dermatol*. 1986;25:103–105.
105. Pappa KA. The clinical development of mupirocin. *J Am Acad Dermatol*. 1990;22:873–879.
106. Bradley SF. Effectiveness of mupirocin in the control of methicillin-resistant *Staphylococcus aureus*. *Infect Med*. 1993;10:23–31.
107. Eltringham I. Mupirocin resistance and methicillin-resistant *Staphylococcus aureus* (MRSA). *J Hosp Infect*. 1997;35:1–8.
108. Smith GE, Kennedy CTC. *Staphylococcus aureus* resistant to mupirocin. *J Antimicrob Chemother*. 1988;21:141–142.
109. Decousser JW, Pina P, Ghnassia JC, et al. First report of clinical and microbiologic failure in the eradication of glycopeptide-intermediate methicillin-resistant *Staphylococcus aureus* carriage by mupirocin. *Eur J Clin Microbiol Infect Dis*. 2003;22:318–319.
110. Cookson BD. Mupirocin resistance in staphylococci. *J Antimicrob Chemother*. 1990;25:497–503.
111. Udo EE, Jacob LE, Mokadas EM. Conjugate transfer of high-level mupirocin resistance from *Staphylococcus haemolyticus* to other staphylococci. *Antimicrob Agents Chemother*. 1997;41:693–695.
112. Mondino PJ, dos Santos KR, de Freire Bastos Mdo C, et al. Improvement of mupirocin E-test for susceptibility testing of *Staphylococcus aureus*. *J Med Microbiol*. 2003;52:385–387.
113. Reshpane LM, Fix AM, Pfaller MA, et al. Emerging elevated mupirocin resistance rates among staphylococcal isolates in the SENTRY antimicrobial surveillance program (2000): correlations of results from disk diffusion, E-test and reference dilution methods. *Diagn Microbiol Infect Dis*. 2002;42:283–290.
114. Booth JH, Benrimo SI. Mupirocin in the treatment of impetigo. *Int J Dermatol*. 1992;31:1–9.
115. Bork K, Brauers J, Kresken M. Efficacy and safety of 2% mupirocin ointment in the treatment of primary and secondary skin infections: an open multicentre trial. *Br J Clin Pract*. 1989;43:284–288.
116. De la Brassinne M, De Bersaques J, Vossaert K, et al. Efficacy of mupirocin 2% ointment in skin infection: Belgian prospective open multicentre study. *Dermatologica*. 1988;177:397–400.
117. Eells LD, Mertz PM, Piovanetti Y, et al. Topical antibiotic treatment of impetigo with mupirocin. *Arch Dermatol*. 1986;122:1273–1276.
118. Wilkinson RD, Carey WD. Topical mupirocin versus topical Neosporin in the treatment of cutaneous infections. *Int J Dermatol*. 1988;27:514–515.
119. Gilbert M. Topical 2% mupirocin versus 2% fusidic acid ointment in the treatment of primary and secondary skin infections. *J Am Acad Dermatol*. 1989;20:1083–1087.
120. Leyden JJ. Review of mupirocin ointment in the treatment of impetigo. *Clin Pediatr*. 1992;31:549–553.
121. Leyden JJ. Mupirocin: a new topical antibiotic. *Semin Dermatol*. 1987;6:48–54.
122. Breneman DL. Use of mupirocin ointment in the treatment of secondarily infected dermatoses. *J Am Acad Dermatol*. 1990;22:886–892.
123. Riu S, Ruiz C, Martinez-Vea C, et al. Spontaneous rupture of polyurethane peritoneal catheter: a possible deleterious effect of mupirocin ointment. *Nephrol Dial Transplant*. 1998;13:1870–1871.

39 Antimycobacterial Agents

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SHORT VIEW SUMMARY

Therapy for Tuberculosis *(Mycobacterium tuberculosis)* (see Chapter 249)

- Isoniazid, rifampin, pyrazinamide, and ethambutol are first-line agents for drug-susceptible tuberculosis. Doses of antiretroviral agents may need adjustment (see Table 39.3).
- Initiation of treatment for human immunodeficiency virus (HIV) infection usually does not need to be delayed in patients starting treatment for tuberculosis (see Table 39.2 and http://aidsinfo.nih.gov/guidelines).
- Rifabutin is used instead of rifampin in patients receiving protease inhibitors and nonnucleoside reverse transcriptase inhibitors for HIV infection (see Table 39.5).
- Rifapentine is recommended for directly observed therapy along with isoniazid, both given once weekly for 12 weeks for latent tuberculosis.
- Fluoroquinolones, amikacin, kanamycin, streptomycin, capreomycin, linezolid, para-aminosalicylic acid, cycloserine, and ethionamide are second-line agents used for drug-resistant *M. tuberculosis* infection. Fluoroquinolones are the most important of these agents.
- Bedaquiline and delamanid are available for drug-resistant tuberculosis.

Therapy for Hansen Disease *(Mycobacterium leprae)* (see Chapter 250)

- Dapsone, rifampin, and clofazimine are first-line agents. Clofazimine use is restricted (see text).

Therapy for Other Mycobacterial Infections

- Macrolides are the most important drugs for treating macrolide-susceptible nontuberculous mycobacteria isolates including *Mycobacterium avium-intracellulare* complex and susceptible *Mycobacterium abscessus* subsp.
- Tetracyclines, macrolides, and quinolones are discussed more extensively in Chapters 26, 29, and 35.

Drugs for mycobacterial infections are discussed in three groups: drugs primarily for the treatment of infections caused by *Mycobacterium tuberculosis,* drugs for infections caused by nontuberculous mycobacteria (NTM), and agents principally for the treatment of Hansen disease (leprosy). Approaches to antituberculous chemotherapy have been affected by the increasing prevalence of multidrug-resistant *M. tuberculosis* (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampin,[1–3,4,5] and extensively drug-resistant *M. tuberculosis* (XDR-TB), defined as resistance to at least INH and rifampin, resistance to any fluoroquinolone, and resistance to at least one second-line injectable drug,[5,6,7,8,9,10] and by the special impact on *M. tuberculosis* of human immunodeficiency virus (HIV) infection.[5,11,12,13]

MDR-TB and XDR-TB strains require the use of drugs that are considered second-line agents as well as drugs that must be administered by injection.[14] The list of agents active against MDR-TB and XDR-TB strains is limited; however, more recent development and introduction of new antituberculous drugs has significantly improved the outlook for successful treatment of *M. tuberculosis* strains resistant to traditional first-line and second-line agents. The current pace of new tuberculosis drug development is unprecedented and cause for optimism even in the presence of increasing MDR-TB and XDR-TB disease prevalence. However, it still must be emphasized that universal supervised therapy is essential to prevent the emergence of acquired drug resistance and to optimally treat both drug-susceptible and drug-resistant *M. tuberculosis* infection.[15,16]

MDR-TB and XDR-TB infections are especially concerning in individuals infected with HIV with or without acquired immunodeficiency syndrome (AIDS) because the host contribution to controlling the infection is severely diminished. HIV-infected patients have a number of other special problems. They are especially prone to adverse drug reactions.[13,17] The susceptibility of protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) to hepatic metabolism induced by rifamycins, especially rifampin and rifapentine, necessitates regimens that exclude these agents.[13,17] In addition, malabsorption of antituberculous drugs can occur in patients with AIDS, resulting in suboptimal antituberculous serum drug levels, which predisposes to acquired drug resistance.[18]

The early years of HIV disease saw a dramatic increase in the prevalence and severity of infections caused by *Mycobacterium avium* and other NTM, especially in their disseminated forms. However, the combination of the macrolide group (clarithromycin and azithromycin) with ethambutol was active against *M. avium* and other NTM even in patients with markedly impaired cell-mediated immune defenses. In recent years, with great advancement in antiretroviral therapy (ART) and the use of disseminated *M. avium* prophylaxis, the incidence of disseminated disease in advanced HIV infection has markedly declined. The effects of HIV infection and AIDS on Hansen disease and its chemotherapy do not appear to be as great as expected.

Traditionally, antimicrobial agents for tuberculosis have been classified as first-line drugs, having superior efficacy with acceptable toxicity, and second-line drugs, having less efficacy and greater toxicity. Several excellent reviews of antimycobacterial agents and therapy are available,[14,19,20,21,22,23,24] including guidelines for therapy for MDR-TB infection.[14,20,21] Effective treatment of both MDR-TB and XDR-TB strains requires detailed information about extended drug susceptibilities to guide individualized treatment regimens.[8,14,20,25]

Antituberculous drugs differ in their mechanism of bactericidal action and in their delivery to tuberculous lesions. Three of the first-line agents—INH, rifampin, and ethambutol—are active against the large populations of tubercle bacilli in cavities. Streptomycin (now considered a second-line agent), other aminoglycosides, and capreomycin penetrate cells poorly and are inactive at acidic pH. Pyrazinamide (PZA), the fourth first-line agent, is inactive at the neutral or slightly alkaline pH that may occur extracellularly and is active only in acidic environments such as within macrophages. Slowly replicating organisms in necrotic foci are killed by rifampin and less readily by INH.

First-line antituberculous agents except ethambutol are bactericidal. The bactericidal activities of both INH and rifampin against tubercle bacilli in cavitary, intracellular, or necrotic foci provide the basis for the efficacy of short-course INH-rifampin regimens. A combination of three bactericidal agents that are active against intracellular organisms—INH, rifampin, and PZA—is essential for the 2-month initiation phase of the standard 6-month regimen currently recommended for drug-susceptible disease in the United States. A residual population consisting

of virtually nonreplicating tubercle bacilli within necrotic foci is especially difficult to eradicate, perhaps explaining the minimum of 4 months of continuation phase therapy needed even in individuals with competent immune defenses.

Much of the following discussion of individual antimycobacterial agents is taken from existing guidelines. In collaboration with other organizations, the US Centers for Disease Control and Prevention (CDC) recently updated treatment guidelines for tuberculosis.[21] Additionally, new technologies such as the widely available tuberculosis GeneXpert and gene sequencing, available through the CDC, offer the clinician the ability to rapidly (within days) detect drug-resistant *M. tuberculosis* strains to limit empirical use of ineffective and toxic second-line tuberculosis medication regimens. The reader is encouraged to contact the CDC website for details about the indications and procedures for using rapid molecular detection of drug resistance identification technologies (http://cdc.gov/tb/topic/laboratory/mddrusersguide).

Chemical structures of the major drugs discussed in this chapter are shown in Fig. 39.1.

FIRST-LINE ANTITUBERCULOUS DRUGS

Isoniazid

Derivation and Structure

Isoniazid, isonicotinic acid hydrazide (INH), a synthetic agent, was introduced in 1952.

Mechanism of Action

INH is bactericidal against actively growing *M. tuberculosis* and bacteriostatic against nonreplicating organisms. It acts by inhibition of synthetic pathways of mycolic acid, an important constituent of mycobacterial cell walls. It also likely inhibits the catalase-peroxidase enzyme coded for by the gene *katG*.

Antimicrobial Activity and Resistance

Against *M. tuberculosis,* 0.025 to 0.05 μg/mL of INH is inhibitory, and higher concentrations are bactericidal against replicating organisms. When INH is administered alone as monotherapy in the presence of active tubercular disease, resistance to INH will emerge. Initially susceptible isolates become resistant in more than 70% of cases treated with INH monotherapy for 3 months. Resistance results from selection under antimicrobial pressure of resistant mutants of *M. tuberculosis* that number 1 in 10^6 among untreated bacillary populations. Large populations such as the 10^9 to 10^{10} bacilli in pulmonary cavities are especially likely to contain significant numbers of inherently resistant tubercle bacilli. Low-level INH resistance, defined as an INH minimal inhibitory concentration (MIC) for *M. tuberculosis* of greater than 0.1 μg/mL but less than 1.0 μg/mL, is most commonly associated with point mutations or short deletions within the catalase-peroxidase gene *(katG)*, which still produces some enzymatic activity, whereas high-level resistance, defined as an INH MIC for *M. tuberculosis* of greater than 1.0 μg/mL, is associated with major deletions within the gene with loss of all enzymatic activity.[26,27] Most experts recommend treating patients with low-level INH resistance in the same manner as if they had higher level in vitro INH resistance with the exception that INH retains sufficient activity in this situation to justify inclusion in the treatment regimen. Resistance in the regulatory region of a second gene involved in mycolic acid synthesis *(inhA)* also confers INH resistance.[26,27] The incidence of INH resistance among new cases of tuberculosis in the United States in 2016 was 8.7%, occurring primarily in people born outside the United States including immigrants from Africa, Southeast Asia,

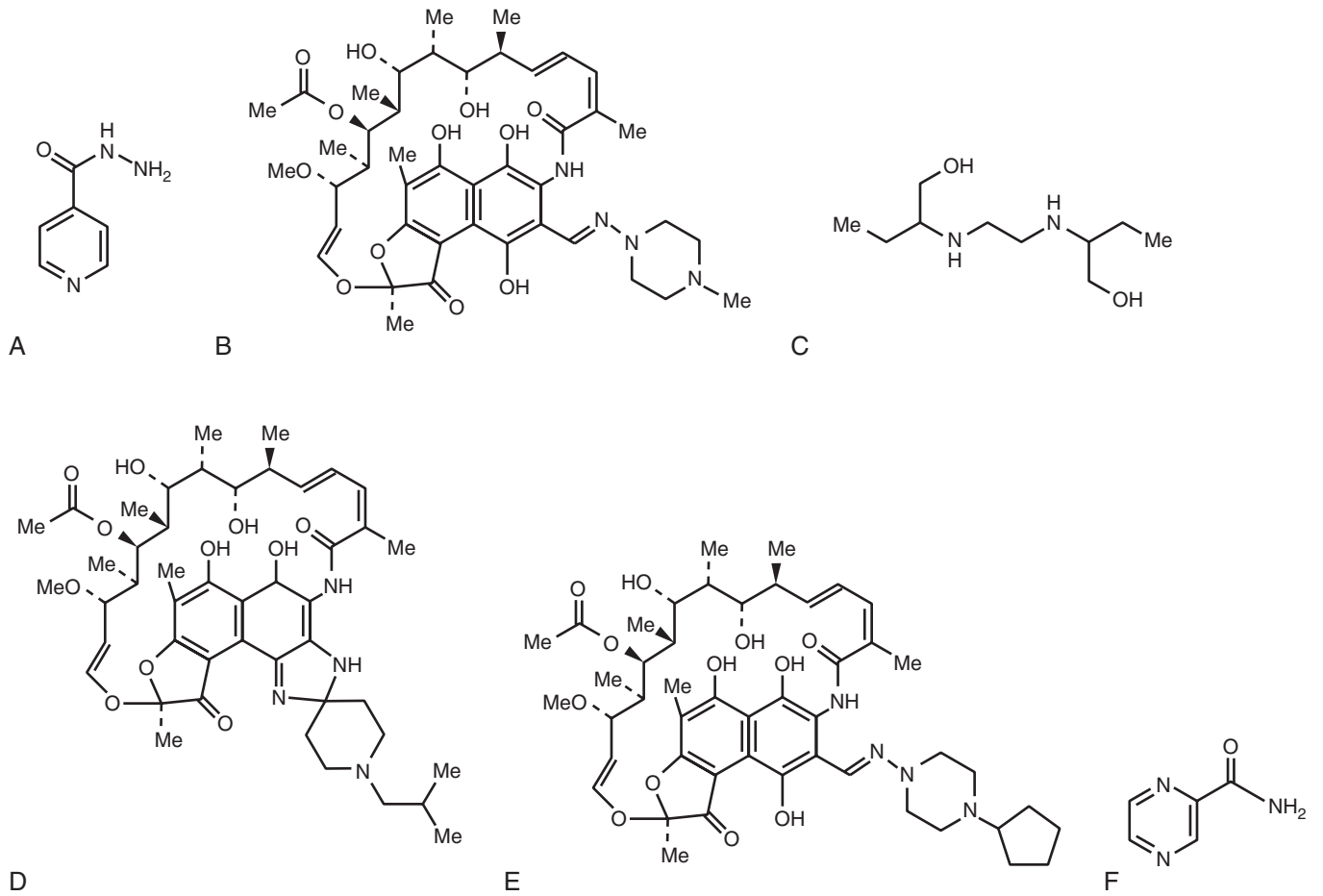

FIG. 39.1 Structures of major antimycobacterial agents. (A) Isoniazid. (B) Rifampin. (C) Ethambutol. (D) Rifabutin. (E) Rifapentine. (F) Pyrazinamide.

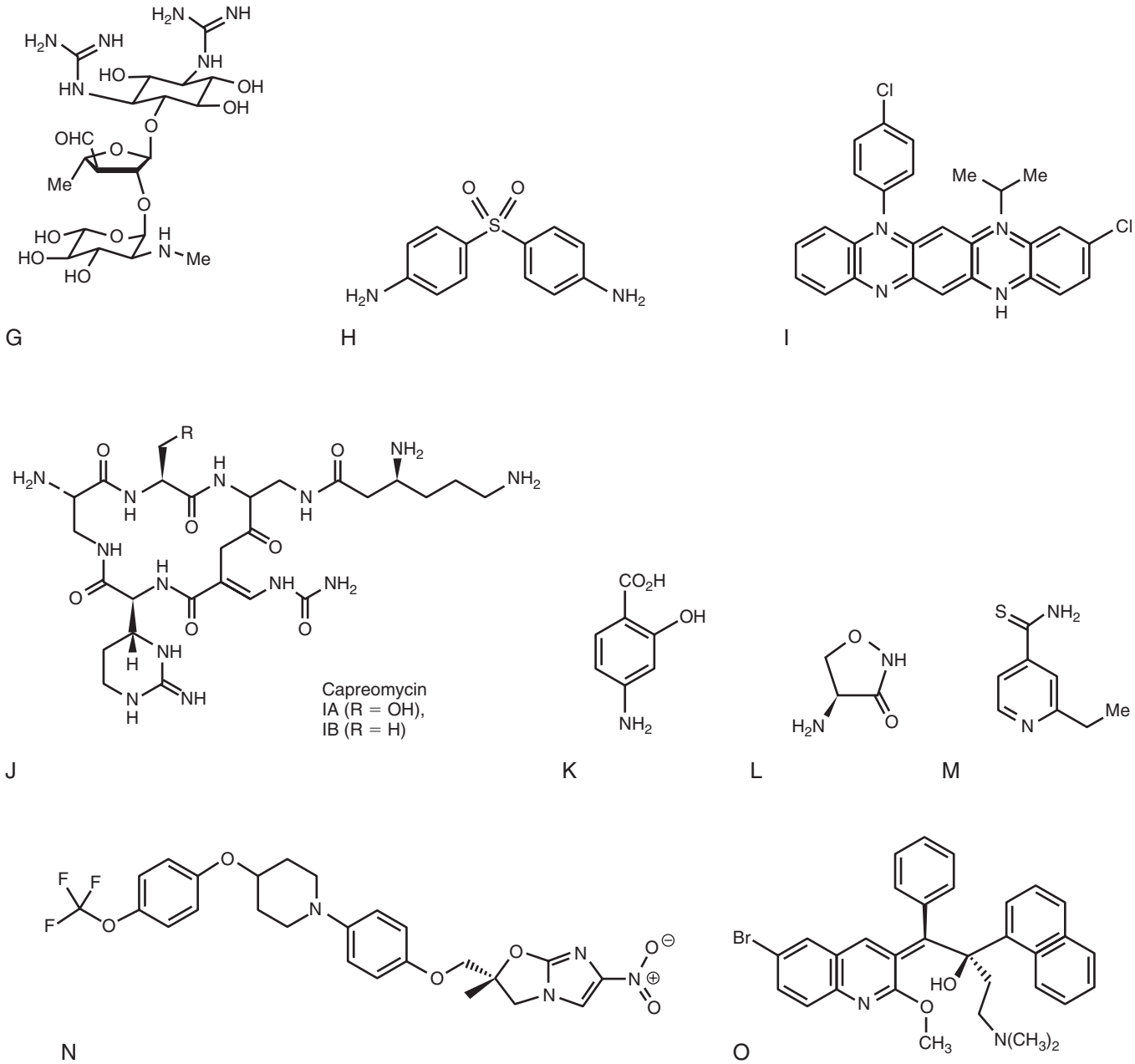

FIG. 39.1, cont'd (G) Streptomycin. (H) Dapsone. (I) Clofazimine. (J) Capreomycin. (K) Para-aminosalicylic acid. (L) Cycloserine. (M) Ethionamide. (N) Delamanid. (O) Bedaquiline.

Eastern Europe, and Central America, where INH resistance is more common.[11,12,28]

Pharmacology

INH is well absorbed orally or intramuscularly and is distributed throughout the body. Cerebrospinal fluid (CSF) levels are generally about 20% of plasma concentrations but may approach plasma levels in the presence of meningeal inflammation. Coadministration with vitamin C appears to inactivate INH suspensions markedly.[29]

Metabolism of INH occurs initially by hepatic *N*-acetyltransferase. Diminished acetylation capacity is inherited as an autosomal recessive trait that varies from a 5% prevalence rate in indigenous people in Canada to 83% in Egyptians. Ten percent to 15% of Asians are "slow" acetylators, as are 58% of whites in the United States. Six hours after a 4-mg/kg oral dose, slow acetylators exhibit plasma INH levels of more than 0.8 µg/mL, and rapid acetylators have levels of less than 0.2 µg/mL.[20] The striking bimodal distribution of plasma half-lives of INH depending on acetylator status generally does not affect the outcome with daily therapy because plasma levels are maintained well above inhibitory concentrations. Metabolically altered INH is principally excreted in urine along with lesser amounts of unaltered drug. Dosage modification in renal insufficiency is not necessary. The benefit of dosage adjustment with significant hepatic disease is not established. Table 39.1 summarizes dosage modifications for INH and other antituberculous drugs in hepatic or renal failure.

Adverse Reactions

Hepatitis. INH has infrequent major toxicities, most notably hepatitis. Of INH recipients, 10% to 20% have asymptomatic minor elevations in serum aspartate aminotransferase levels that usually resolve even with continued therapy.[30] A meta-analysis of six studies estimated the rate of clinical (symptomatic) hepatitis in patients given INH alone to be approximately 0.6%.[31] More recent data indicate that the incidence of clinical hepatitis is even lower. Hepatitis occurred in

TABLE 39.1 Need for Dosage Modification for Antituberculous Drugs in Hepatic or Renal Failure

ANTIMICROBIAL DRUG	MODIFY IN HEPATIC FAILURE	MODIFY IN RENAL FAILURE
Isoniazid	No	No
Pyrazinamide	Yes	Yes
Ethambutol	No	Yes
Rifampin	?Yes	No
Rifabutin	?Yes	No
Amikacin	No	Yes
Capreomycin	No	Yes
Kanamycin	No	Yes
Streptomycin	No	Yes
Quinolones	No	Yes (levofloxacin, not moxifloxacin)
Para-aminosalicylic acid	No	Yes
Ethionamide	Yes	No
Cycloserine	No	Yes

only 0.1% to 0.15% of 11,141 patients receiving INH alone as treatment for latent tuberculosis infection (LTBI) in an urban tuberculosis control program.[32]

Early estimates of the incidence of severe or major INH hepatotoxicity were provided from the results of a large multicenter US National Institutes of Health (NIH)–sponsored trial. Fatal hepatitis occurred in 8 of nearly 14,000 patients receiving INH.[33] All but one of the deaths occurred in one study center, and patients did not receive routine monitoring for toxicity during the trial.[33] More recent studies, however, suggest that the rate of fatal INH-related hepatitis is substantially lower.[32,34,35] The likely explanation is the adoption in the early 1980s of uniform clinical toxicity monitoring for patients receiving INH for treatment of LTBI.[34,35] Hepatotoxicity can occur at any time but generally occurs after weeks to months of therapy rather than days to weeks after treatment has begun. INH hepatotoxicity is correlated with age, presumably owing to a diminished capacity for repair of INH-induced hepatocellular damage in elderly patients. Undernutrition may also play a role in the expression of INH hepatotoxicity.[36] Hepatotoxicity is increased in the following groups: patients who abuse alcohol, patients with preexisting liver damage,[33] pregnant women and women up to 3 months postpartum,[37] patients also taking INH in combination with acetaminophen,[38] patients receiving other potentially hepatotoxic agents such as rifampin,[35] patients with active hepatitis B, and HIV-seropositive patients receiving highly active antiretroviral therapy (HAART).[39] Histologically, hepatocellular damage can progress to submassive necrosis. Although active hepatitis B is considered a contributing factor to INH hepatotoxicity,[40,41] INH has been safely administered to patients with acute hepatitis[42] and for LTBI to patients with chronic hepatitis B and C infection.[39,43,44] Educating patients about the recognition of symptoms of INH-induced liver disease is key in preventing its progression. As noted, routine clinical monitoring of patients receiving INH is mandatory.[35]

Routine monitoring of serum hepatic enzyme concentrations is not indicated for all patients at the start of treatment of LTBI. Baseline testing is recommended for patients whose initial evaluation suggests a liver disorder, patients infected with HIV who are receiving HAART, pregnant women and women in the immediate postpartum period (i.e., within 3 months of delivery), patients with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), individuals who use alcohol regularly, and other individuals who are at risk for chronic liver disease.[35,39] Baseline testing is no longer routinely indicated in people older than 35 years of age.[35,39] Laboratory monitoring during treatment of LTBI is indicated for patients whose baseline liver function test results are abnormal and for other individuals at risk for hepatic disease.[35,39,45] Although biochemical monitoring may contribute to patient confidence and adherence with the treatment regimen, the contribution of routine biochemical monitoring to the safety of INH administration is not proven. The importance of routine clinical monitoring is clear, however, and clinical monitoring must be applied rigorously with or without biochemical monitoring.

The most feared INH-related toxicity is fulminant hepatic failure necessitating liver transplantation or resulting in death. The CDC conducted a detailed analysis of 17 patients with severe INH-related hepatotoxicity over a 4-year period.[46] The estimated incidence of death and liver transplantation was 1 in 150,000 to 1 in 220,000 patients receiving INH therapy for LTBI. Although continuation of INH after the onset of hepatitis-related symptoms was associated with severe hepatotoxicity, some patients still developed severe hepatotoxicity after stopping INH within days to a week of symptom onset. Although it is not universally protective, patients should be strongly advised to discontinue INH therapy at the onset of symptoms consistent with incipient hepatitis such as nausea, loss of appetite, and abdominal pain. Perhaps most disconcerting, there were two children younger than 15 years of age in this series of patients. The overall conclusions of this analysis were that severe hepatotoxicity was idiosyncratic, occurred at any time during INH treatment, occurred even with careful clinical and biochemical monitoring and with appropriate (recommended) doses of INH, and could occur in children.[46]

Most hepatotoxicity subsides after discontinuation of INH. Cautious readministration of INH after resolution of hepatitis for selected patients has been reported to be well tolerated and safe,[47] although most experts recommend alternative therapies such as rifampin for LTBI.[35,39] Recognition of the frequency and severity[48] of INH hepatotoxicity has not curtailed therapeutic usage but has led to a revision of indications for treatment of LTBI, with special caution indicated for groups identified at high risk for INH hepatotoxicity (see earlier discussion).[35,39,48]

Neurotoxicity. Peripheral neuropathy has been described in 17% of recipients of 6 mg/kg/day of INH but is less frequent when adults receive the standard dose of 300 mg/day. Poor nutrition or underlying alcoholism, diabetes mellitus, or uremia predisposes to neuropathy, which is more frequent in slow acetylators who have higher plasma levels of unaltered drug. Increased pyridoxine excretion is promoted by INH. Pyridoxine 10 to 50 mg daily can ameliorate neuropathy without interfering with the antimycobacterial effect. Current guidelines suggest that use of pyridoxine is necessary only for patients with underlying predispositions for neuropathy, as outlined earlier, but pyridoxine use is essentially universal for patients receiving INH. Notably, neuropathy is a manifestation of excessive pyridoxine dosing.

INH-induced central nervous system (CNS) toxicity can produce aberrations ranging from memory loss to psychosis or seizures. Optic neuropathy has been reported and can be confused with ethambutol-related optic neuritis in patients receiving both drugs. Toxic CNS reactions are not necessarily related to pyridoxine deficiency but have responded to pyridoxine administration.[20]

Hypersensitivity reactions. Fever, which may be sustained or "spiking"; skin eruptions; and hematologic abnormalities can occur. INH recipients can develop positive antinuclear antibody reactions and rarely manifest a lupus-like syndrome that is reversible on discontinuation of INH.

Miscellaneous adverse reactions. INH-associated arthritic disorders have included Dupuytren contracture and shoulder-hand syndrome.[20,24] Pellagra can occur in malnourished INH recipients.[20,49] Pyridoxine deficiency–related anemia can occur in children or adults.[50]

Overdose

Accidental ingestion of INH by children or ingestion during a suicide attempt may result in metabolic acidosis, hyperglycemia, seizures, and coma. High-dose pyridoxine usually reverses these toxicities.

Significant Drug Interactions

Particular caution is indicated when administering INH to patients with a seizure disorder. INH may alter metabolism of antiseizure medications, so it is important to monitor blood levels of seizure medications for patients taking INH. Phenytoin (Dilantin) toxicity is potentiated by INH. Mental changes, nystagmus, and ataxia can result,

especially in slow acetylators whose high INH levels inhibit phenytoin metabolism. Concomitant use of INH with valproic acid may result in increased serum concentrations of valproic acid and increase the risk for serious adverse reactions such as hepatotoxicity. Theophylline toxicity has been reported with coadministration of INH. INH decreases the efficacy of clopidogrel by decreasing the metabolism of the parent compound to the more biologically active metabolite. Combined INH and rifampin therapy predisposes to elevation of plasma hepatic enzymes. Plasma INH concentrations are increased by para-aminosalicylic acid (PAS) through interference with acetylation. Although significant drug interactions are less frequent with INH than with rifampin, it is important to check for all potential drug-drug interactions for any patient taking INH.

Usage

INH is indicated for all clinical forms of tuberculosis. It is used alone for therapy for LTBI in individuals with selected purified protein derivative skin test or interferon-γ release assay reactions at high risk for developing active tuberculosis disease.[35] The most recent American Thoracic Society (ATS)/CDC/Infectious Diseases Society of America (IDSA) guidelines state that INH is considered safe in pregnancy, but the risk for hepatitis may be increased both before and after delivery. Supplementation with pyridoxine is recommended if INH is administered during pregnancy.[19,35] INH is approved by the US Food and Drug Administration (FDA) for treating active tuberculosis in pregnant patients, but it should be given with caution and then only for selected high-risk patients with LTBI (e.g., HIV-seropositive patients or recent contacts to individuals with active tuberculosis).[35]

Availability and Dosage

INH is available generically (tablets, syrup, injectable solutions) and under brand names (INH tablets or Nydrazid injection solution). Dosage forms include 100-mg and 300-mg tablets, syrup containing 10 mg/mL, 100 mg/mL solution for parenteral injection, and combination capsules combining 150 mg of INH with 300 mg of rifampin (Rifamate) or tablets of 50 mg with 120 mg of rifampin and 300 mg of PZA (Rifater). The usual adult dosage is 5 mg/kg/day (preferably 300 mg once daily). A higher dosage (10–15 mg/kg; maximum 300 mg/day) has been recommended for infants and children.

With directly observed therapy for all patients, the initial induction phase of drug-susceptible tuberculosis includes INH, rifampin, and PZA, preferably given daily for the entire 2-month induction phase of therapy. Intermittent, three-times-weekly, high-dose INH, 15 mg/kg orally (maximum 900 mg), combined with rifampin, 10 mg/kg (maximum 600 mg orally), can be given for the maintenance phase of drug-susceptible tuberculosis therapy. Multiple therapeutic options are available with the caveat that the more drug that is administered, the better the outcome. For most patients in the United States with tuberculosis, these drugs are combined with ethambutol during the induction phase of therapy until susceptibilities are available. A reliable urine test is available to confirm INH ingestion.[51] Although the preferred parenteral route is intramuscular injection, INH for injection can be administered safely intravenously.[52]

Rifampin (see also Chapter 27)

Derivation and Structure

Rifampin (termed *rifampicin* in the United Kingdom) is a semisynthetic derivative of a complex macrocyclic antibiotic, rifamycin B, produced by *Streptomyces mediterranei*. It was introduced for clinical trials in tuberculosis in 1967.

Mechanism of Action

Rifampin inhibits DNA-dependent RNA polymerase. Human RNA polymerase is insensitive.

Antimicrobial Activity and Resistance

Rifampin is bactericidal against actively replicating *M. tuberculosis* to a degree comparable to INH with MICs of 0.005 to 0.2 μg/mL. It is also active against intracellular, slowly replicating bacilli and somewhat against nearly dormant organisms in necrotic foci. Efficacy of rifampin is indicated in susceptible pulmonary tuberculosis by sputum conversion 2 weeks earlier with rifampin-containing regimens than with regimens without the drug. Resistance emerges rapidly if the drug is given as monotherapy. Approximately 95% of resistance to rifampin results from a point mutation or deletion within an 81–base pair region of the gene encoding the β-subunit of RNA polymerase *(rpoB)*.[27,53] Mutations in the *rpoB* gene can be rapidly detected with the tuberculosis GeneXpert technology, which is widely available in the United States. The prevalence of rifampin resistance among new cases of tuberculosis in the United States is currently less than 1%.[11,12] In the past, isolated rifampin resistance in the United States was strongly associated with HIV infection.[54] However, currently in the United States, the discovery of rifampin resistance by GeneXpert analysis, available before phenotypic drug susceptibility results, should be considered an indicator for MDR-TB. Isolates with *rpoB* mutations should be immediately referred to the CDC for molecular detection of drug resistance analysis to detect mutations associated with resistance to other antituberculosis drugs, especially INH. Resistance to rifampin is associated in all instances with cross-resistance to rifapentine and in most instances with rifabutin, especially in the presence of high-level resistance. Rifampin resistance coupled with resistance to INH and other antituberculous agents defines either MDR-TB or XDR-TB isolates, depending on the number and type of antituberculous agents to which the *M. tuberculosis* isolate is resistant.[5,14]

Pharmacology

Rifampin is well absorbed orally, yielding peak plasma concentrations of 7 to 8 μg/mL after a dose of 600 mg. It is widely distributed throughout the body. CSF concentrations range from undetectable to 0.5 μg/mL in healthy individuals and reach 50% of plasma concentrations with meningeal inflammation. The high lipid solubility of rifampin enhances phagosomal penetration. Rifampin is deacetylated to an active form that undergoes biliary excretion and enterohepatic recirculation. Because of autoinduction of rifampin metabolism (cytochrome P-450–coupled),[55] biliary excretion increases with continued therapy. Induction of rifampin's metabolism with consequent reduction in its half-life and plasma concentrations becomes maximal after approximately six doses.[56] Excretion is primarily into the gastrointestinal tract, with lesser amounts excreted in the urine. The plasma concentration and urinary excretion increase in hepatic failure. Probenecid blocks hepatic uptake, causing decreased biliary excretion. There are no recommendations for rifampin dosage modification (i.e., dose reduction) with either hepatic or renal insufficiency. Rifampin is not removed by hemodialysis or peritoneal dialysis.[57]

Adverse Reactions

Minor adverse reactions are frequent with rifampin, but cessation of therapy because of adverse effects was necessary in only 6 of 372 patients taking the drug for 20 weeks.[58]

Hepatitis. The major adverse effect of rifampin is hepatitis. Minimal abnormalities in liver function tests are common in patients taking rifampin and usually resolve, possibly because of autoinduction of its metabolism even with continuation of the drug. Characteristically, elevations of bilirubin and alkaline phosphatase levels result, whereas elevation of hepatocellular enzyme concentrations can be caused by rifampin, INH, or both. Patients who abuse alcohol with preexisting liver damage appear to be especially prone to rifampin-induced liver reactions. There is no clear evidence that rifampin monotherapy for LTBI is associated with fulminant hepatic failure as reported with INH therapy for LTBI.

Effects on immune parameters. Rifampin has widespread effects on humoral and cell-mediated immunity, but they appear to be of no clinical significance.

Hypersensitivity reactions. Flushing, fever, pruritus without rash, urticaria, cutaneous vasculitis, eosinophilia, thrombocytopenia, hemolysis, or renal failure due to interstitial nephritis can occur with rifampin use. A systemic flulike syndrome, at times associated with thrombocytopenia, has been described almost exclusively with intermittent, high-dose therapy.

Miscellaneous adverse reactions. Widespread distribution of rifampin is reflected in an orange color appearing in urine, feces, saliva,

sputum, pleural effusions, tears, soft contact lenses, sweat, semen, and CSF. With overdosage, red man syndrome of skin discoloration has been described. Gastrointestinal upset is frequent but is usually ameliorated by a temporary reduction in dosage.

Significant Drug Interactions

By induction of microsomal cytochrome P-450–mediated enzymatic activities, rifampin causes increased hepatic metabolism of many substances. Rifampin interaction with more than 100 drugs has been described.[13,17,59–61] Despite interactions with many antiretroviral agents, rifampin or rifabutin is an essential component of treating tuberculosis in HIV-infected patients (Table 39.2). A compilation of this expanding list of compounds is given in Table 39.3. The induction period with rifampin may last for weeks after the drug is discontinued. The recent introduction of PIs and NNRTIs for the treatment of HIV infection has complicated the treatment of tuberculosis in this setting (see Table 39.3). Because rifampin induces metabolism of PIs and NNRTIs, rifampin should not be coadministered with these agents.[13,17,62] The most recent guidelines for coadministration of rifamycins with antiretroviral agents are summarized in Table 39.3 and can be found on the NIH website (http://aidsinfo.nih.gov/guidelines),[13] which is a living document with ongoing updates. Assistance can also be found at the CDC website (www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm).[17] As new antiretroviral agents and more pharmacokinetic data become available, treatment recommendations are likely to be modified, so the reader is encouraged to check these websites periodically for updates.

In general, the coadministration of antituberculosis drugs and antiretroviral drugs should be initiated and guided by clinicians experienced in the treatment of these patients and familiar with the potential drug-drug interactions.

Competition for excretion with contrast agents used for biliary tract imaging may cause inability to visualize the gallbladder. Probenecid interferes with renal excretion, whereas PAS may interfere with gastrointestinal absorption.

Usage

Rifampin is indicated for treatment of all forms of pulmonary and extrapulmonary tuberculosis. It is recommended for treatment of LTBI as an alternative choice to INH.[35] The available data suggest that the efficacy of rifampin for treating LTBI appears comparable to that of INH, and, as noted, it appears to be less frequently associated with severe hepatotoxicity. Rifampin in combination with PZA was shown to be effective in HIV-positive patients for LTBI therapy when given for only 2 months,[63] but for reasons that have yet to be elucidated, the combination of rifampin and PZA for treatment of LTBI was associated with an unanticipated high rate (almost 6%) of severe or fatal hepatotoxicity, especially in HIV-seronegative patients.[64,65] Therefore the combination of rifampin and PZA is not currently recommended for treatment of LTBI, although the use of this regimen might rarely be indicated for selected patients under unusual circumstances with close clinical and biochemical monitoring and supervision by experienced clinicians. Rifampin is approved by the FDA for use in pregnant patients with active tuberculosis. As with INH, it should be used in pregnancy only for high-risk patients with LTBI and then only if INH is not appropriate.

Availability and Dosage

Rifampin is supplied in the United States as Rifadin, available in 150-mg or 300-mg capsules and in combination 300-mg capsules with 150 mg of INH (Rifamate) or 120-mg tablets with 50 mg of INH and 300 mg of PZA (Rifater). Rifampin from opened capsules can be suspended (usually 10 mg/mL) in simple or flavored sugar syrups that should not include ascorbic acid, which can inactivate rifampin.[29] Suspensions can be refrigerated up to 2 weeks. Rifampin for intravenous infusion (600 mg/vial; Rifadin) should not be administered intramuscularly. The usual oral dosage is 10 mg/kg/day (maximum 600 mg) for adults and 10 to 20 mg/kg/day for children (not to exceed 600 mg/day). A 600-mg twice-weekly schedule generally has been well tolerated. The current rifampin dosing recommendations have raised concerns that some patients may be receiving suboptimal rifampin doses.[66] For instance, with current recommendations for 10 mg/kg/dose, maximal 600 mg, dosing, a 60-kg individual would receive the same rifampin dose as a 100-kg person. One study has shown that doses of 35 mg/kg/day are safe and well tolerated, with ongoing studies investigating the efficacy of weight-adjusted rifampin doses higher than the 600-mg dose. The most recent ATS/CDC/IDSA tuberculosis treatment guidelines still recommend a maximal rifampin dose of 10 mg/kg/dose with latitude for the prescribing physician to increase the dose on an individualized basis.[66a]

Pyrazinamide

Derivation and Structure

PZA is a synthetic pyrazine analogue of nicotinamide.

TABLE 39.2 *Mycobacterium tuberculosis* Disease in Human Immunodeficiency Virus (HIV) Coinfection

- The principles for treatment of active tuberculosis (TB) disease in HIV-infected patients are the same as those for HIV-uninfected patients.
- All HIV-infected patients with diagnosed active TB should be started on TB treatment as soon as possible.
- All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART).
- In patients with CD4 counts <50 cells/mm^3, ART should be initiated within 2 weeks of starting TB treatment.
- In patients with CD4 counts ≥50 cells/mm^3 who present with clinical disease of major severity as indicated by clinical evaluation (including low Karnofsky score, low body mass index, low hemoglobin, low albumin, organ system dysfunction, or extent of disease), ART should be initiated within 2–4 weeks of starting TB treatment. The strength of this recommendation varies on the basis of CD4 cell count:
  - CD4 count 50–200 cells/mm^3 (BI)
  - CD4 count >200 cells/mm^3 (BIII)
- In patients with CD4 counts ≥50 cells/mm^3 who do not have severe clinical disease, ART can be delayed beyond 2–4 weeks of starting TB therapy but should be started within 8–12 weeks of TB therapy initiation. The strength of this recommendation also varies on the basis of CD4 cell count:
  - CD4 count 50–500 cells/mm^3 (AI)
  - CD4 count >500 cells/mm^3 (BIII)
- In all HIV-infected pregnant women with active TB, ART should be started as early as feasible, both for maternal health and for prevention of mother-to-child transmission of HIV.
- In HIV-infected patients with documented multidrug-resistant and extensively drug-resistant TB, ART should be initiated within 2–4 weeks of confirmation of TB drug resistance and initiation of second-line TB therapy.
- Despite pharmacokinetic drug interactions, a rifamycin (rifampin or rifabutin) should be included in TB regimens for patients receiving ART, with dosage adjustment if necessary.
- Rifabutin is the preferred rifamycin to use in HIV-infected patients with active TB disease on a protease inhibitor (PI)–based regimen because the risk for substantial drug interactions with PIs is lower with rifabutin than with rifampin (AII).
- Coadministration of rifampin and PIs (with or without ritonavir boosting) is not recommended (AII).
- Rifapentine is *not* recommended in HIV-infected patients receiving ART for treatment of latent TB infection or active TB, unless in the context of a clinical trial (AIII).
- Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).
- Treatment support, which can include directly observed therapy of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).

Rating of recommendations: A = strong; B = moderate; C = optional.
Rating of evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion.
Modified from Department of Health and Human Services: Guidelines for the Use of Antiretroviral Agents in HIV-1 Adolescents and Adults. Last updated July 14, 2016. For the most up-to-date guidelines, see http://aidsinfo.nih.gov/guidelines.

TABLE 39.3 Recommendations for Coadministering Antiretroviral Drugs With Rifampin

	RECOMMENDED CHANGE IN DOSE OF ANTIRETROVIRAL DRUG	RECOMMENDED CHANGE IN DOSE OF RIFAMPIN	COMMENTS
Nonnucleoside Reverse Transcriptase Inhibitors			
Efavirenz	None (some experts recommend 800 mg for patients >60 kg)	No change (600 mg/day)	Efavirenz AUC ↓ by 22%; no change in rifampin concentration. Efavirenz should not be used during first trimester of pregnancy
Nevirapine	Nevirapine and rifampin should not be used together	Nevirapine AUC ↓ 37%–58% and C_{min} ↓ 68% with 200 mg twice daily	
Rilpivirine	Rifampin and rilpivirine should not be used together	Rilpivirine AUC ↓ by 80%	
Etravirine	Etravirine and rifampin should not be used together	Marked decrease in etravirine predicted, based on data on interaction with rifabutin	
Single PIs			
Ritonavir	Rifampin and ritonavir should not be used together		Significantly ↓ PI exposure (>75%) despite ritonavir boosting
Fosamprenavir	Rifampin and fosamprenavir should not be used together		
Atazanavir	Rifampin and atazanavir should not be used together		Atazanavir AUC ↓ by >95%
Indinavir	Rifampin and indinavir should not be used together		Indinavir AUC ↓ by 89%
Nelfinavir	Rifampin and nelfinavir should not be used together		Nelfinavir AUC ↓ by 82%
Saquinavir	Rifampin and saquinavir should not be used together		Saquinavir AUC ↓ by 84%
Dual PI Combinations			
Saquinavir/ritonavir	Saquinavir 400 mg + ritonavir 400 mg twice daily	No change (600 mg/day)	Use with caution; combination of saquinavir (1000 mg twice daily), ritonavir (100 mg twice daily), and rifampin caused unacceptable rates of hepatitis among healthy volunteers
Lopinavir/ritonavir (Kaletra)	Increase dose of lopinavir/ritonavir (Kaletra) to 4 tablets (200 mg of lopinavir with 50 mg of ritonavir) twice daily	No change (600 mg/day)	Use with caution; this combination resulted in hepatitis in all adult healthy volunteers in an initial study
"Super-boosted" lopinavir/ritonavir (Kaletra)	Lopinavir/ritonavir (Kaletra)—2 tablets (200 mg of lopinavir with 50 mg of ritonavir) + 300 mg of ritonavir twice daily	No change (600 mg/day)	Use with caution; this combination resulted in hepatitis among adult healthy volunteers. There are favorable pharmacokinetic and clinical data among young children
Atazanavir/ritonavir	Standard dose of ritonavir-boosted atazanavir (300 mg once daily with 100 mg of ritonavir) should not be used with rifampin	Atazanavir trough concentration ↓ by >90%	
Tipranavir/ritonavir	Rifampin and tipranavir/ritonavir should not be used together		
Darunavir/ritonavir	Rifampin and darunavir/ritonavir should not be used together		
CCR-5 Receptor Antagonists			
Maraviroc	Increase maraviroc to 600 mg twice daily	No change (600 mg/day)	Maraviroc C_{min} ↓ by 78%. No reported clinical experience with ↑ dose of maraviroc with rifampin
Integrase Inhibitors			
Raltegravir	No change	No change (600 mg/day)	Increase raltegravir dose to 800 mg orally twice daily; monitor for antiretroviral efficacy or switch to rifabutin
Dolutegravir	Double dose from 50 mg once daily to 50 mg twice daily	No change	Limited experience
Elvitegravir/cobicistat/ tenofovir/emtricitabine (Stribild)	Coadministration should be avoided		Cobicistat and elvitegravir concentrations may be significantly ↓. Consider alternative antimycobacterial or alternative antiviral regimen

AUC, Area under the curve; C_{min}, trough concentration; *PI,* protease inhibitor.
Modified from UpToDate, 2013. For the most up-to-date information, see http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

Mechanism of Action

The mechanism of action of PZA is unknown.

Antimicrobial Activity and Resistance

PZA is bactericidal for tubercle bacilli at 12.5 µg/mL. Its optimal activity appears to be against semidormant organisms in an acid pH environment, such as that existing intracellularly in phagolysosomes. Despite good activity at acid pH in vitro and inhibitory concentrations within monocytes,[67] PZA exhibits low activity alone in pretreated macrophages.[68] Resistance rapidly evolves if PZA is used alone. Primary resistance is seen in less than 1% of isolates, but nearly 50% of MDR-TB isolates resistant to INH and rifampin are resistant to PZA.[2] Most isolates resistant to PZA have mutations in the gene encoding