Therapeutic Class Review
Third Generation Cephalosporins

Therapeutic Class

- **Overview/Summary:** The cephalosporin family of antibiotics is part of a larger group known as β-lactam antibiotics. Agents within this group share the structural feature of a β-lactam ring. The β-lactam antibiotics are generally considered bactericidal and work by inactivating enzymes involved with bacterial cell wall synthesis.[1] Cephalosporins cover a wide range of organisms and are frequently used antibacterial agents due to their spectrum of activity and ease of administration.[2] Cephalosporins are grouped into generations, based on their spectrum of activity. The first generation cephalosporins are active against gram-positive aerobes but are inactive against penicillin-resistant pneumococci. They typically have poor activity against gram-negative organisms, though some strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Shigella* may be susceptible. Second generation cephalosporins have greater activity against *Haemophilus influenza* compared to the first generation cephalosporins and have enhanced activity against gram-negative bacteria in vitro. Third generation cephalosporins are active against streptococci, *Haemophilus influenza* and *Moraxella catarrhalis* and are more active against gram-negative bacilli compared to first or second generation cephalosporins; however, they are not as active against susceptible strains of staphylococci compared to first generation cephalosporins. Among the orally available third generation cephalosporins, cefpodoxime proxetil and cefdinir have more activity against staphylococci compared to cefixime and ceftibuten, while ceftibuten is weakly active against pneumococci. Its spectrum of activity is similar to cefdinir and cefpodoxime.[2,3] Fourth generation cephalosporins have enhanced activity against gram-negative bacteria compared to the first and second generation cephalosporins and have activity in vitro against gram-negative bacteria that are typically resistant to the third generation cephalosporins, including *Pseudomonas aeruginosa* and Enterobacteriaceae. In addition, they may be more active against gram-positive bacteria compared to some third generation cephalosporins. The only fourth generation cephalosporin is cefepime, which is only available parenterally. As a family, cephalosporins have poor activity against enterococci, Listeria and oxacillin-resistant staphylococci.[2,3] The cephalosporins reach therapeutic levels in urine and in pleural, pericardial, peritoneal and synovial fluid. With the exception of cefuroxime, the first and second generation cephalosporins are not able to effectively penetrate the cerebrospinal fluid and therefore should not be used to treat central nervous system infections. Conversely, the third generation cephalosporins do effectively penetrate the cerebrospinal fluid.[2]

Table 1. Current Medications Available in the Class[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Cefdinir*	Acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis, community-acquired pneumonia, otitis media, pharyngitis and/or tonsillitis, skin and skin structure infections	Capsule: 300 mg Powder for oral suspension: 125 mg/5 mL 250 mg/5 mL	a
Cefditoren (Spectracef®*)	Acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, pharyngitis and/or tonsillitis, skin and skin structure infections	Tablet: 200 mg 400 mg	a
Cefixime (Suprax®)	Acute bacterial exacerbations of chronic bronchitis, acute bronchitis, otitis media, pharyngitis and/or tonsillitis, uncomplicated gonorrhea, urinary tract infections	Powder for oral suspension: 100 mg/5 mL 200 mg/5 mL	-

		Tablet: 400 mg	
Cefpodoxime*	Acute ano-rectal infections in women, acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis, community-acquired pneumonia, otitis media, pharyngitis and/or tonsillitis, skin and skin structure infections, uncomplicated gonorrhea, urinary tract infections	Powder for oral suspension: 50 mg/5 mL 100 mg/5 mL Tablet: 100 mg 200 mg	a
Ceftibuten (Cedax®)	Acute ano-rectal infections in women, otitis media, pharyngitis and/or tonsillitis	Capsule: 400 mg Powder for oral suspension: 90 mg/5 mL 180 mg/5 mL	-

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Studies evaluating the third generation cephalosporins for the treatment of acute exacerbations of chronic bronchitis have not consistently demonstrate significant differences in clinical response or eradication rate when compared to other cephalosporin agents.[13-18]
- Verghese and colleagues compared cefixime and cephalexin in the treatment of hospitalized patients with exacerbations of chronic bronchitis and demonstrated significantly better clinical cure rates in patients treated with cefixime compared to cephalexin (70.8 vs 50.0%; *P*<0.05). The incidence of diarrhea was higher in the cefixime group.[19]
- In the treatment of gonorrhea, cefixime and cefpodoxime have generally demonstrated comparable efficacy in the rate of bacteriologic cure (>90%) in open-label and dose-response studies, while cefixime has been shown to have comparable efficacy when compared to ceftriaxone.[20-24]
- Asmar et al compared cefixime and cefpodoxime in the treatment of acute otitis media. By day 15, the a bacteriologic cure was reported in 83 and 81% of patients treated with cefpodoxime and cefixime, respectively (*P*=0.541).[25]
- Third generation cephalosporins have demonstrated their efficacy in the treatment of bacterial infections of acute bronchitis, chancroid and genital tract infections. [44-46] Other head-to-head studies of the third generation cephalosporins in the treatment of acute otitis media demonstrated no statistically significant differences in efficacy between the agents.[47-50]
- Studies evaluating the use of the third generation cephalosporins for the treatment of pharyngitis and/or tonsillitis have failed to consistently demonstrate "superiority" of any third generation cephalosporins over penicillin or amoxicillin.[26-33]
- In the treatment of lower respiratory tract infections including community-acquired pneumonia, no cephalosporin consistently demonstrated significant differences when the third generation cephalosporins were compared with each other or with cephalosporins in other generations.[34-36]
- Studies evaluating the treatment of skin and soft tissue infections, sinusitis and urinary tract infections did not consistently demonstrate the "superiority" of any third generation cephalosporins when compared with in-class or with other cephalosporins in other generations.[37-43]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Treatment guidelines identify third generation cephalosporins as alternative empiric agents for the treatment of community-acquired pneumonia, and as treatment options for infections due to *Enterobacteriaceae*.[51,52]

- Third generation cephalosporins are considered alternative agents for the treatment of otitis media in patients with non-type 1 penicillin allergies and second-line agents for the treatment of sinusitis due to penicillin and sulfamethoxazole/trimethoprim resistant bacteria or in patients with non-type 1 penicillin allergies.[53,54]
- Cefixime is considered a second-line agent for the treatment of gonorrhea after ceftriaxone.[55]
- The Global Initiative for Chronic Obstructive Lung Disease recommends the use a second or third generation cephalosporin as an alternative to penicillin, ampicillin, amoxicillin, tetracycline or sulfamethoxazole/trimethoprim in patients with chronic obstructive pulmonary disease and mild exacerbations with no risk of a poor outcome.[56]
- For specific recommendations from current consensus guidelines, please refer to the full therapeutic class review.

· Other Key Facts:

- Currently cefixime (Suprax®) and ceftibuten (Cedax®) are only available as branded agents. All other third generation cephalosporins are available generically in at least one dosage form or strength.
- Only third generation cephalosporins that are available in an oral formulation are included within this review.

References

1. Calderwood S. Overview of the beta-lactam antibiotics. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Jul 31]. Available from: http://www.utdol.com/utd/index.do.
2. Calderwod S. Cephalosporins. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2010 [cited 2012 Jul 31]. Available from: http://www.utdol.com/utd/idex.do.
3. Antiinfectives 8:00, Antibacterials 8:12, Cephalosporins 8:12.06. In: McEvoy GK ed. American Hospital Formulary Services, AHFS Drug Information 2011 [monograph on the internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2012 [cited 2012 Jul 31]. Available from: http://online.statref.com.
4. Cefdinir capsules [package insert]. Sellersville (PA): Teva Pharmaceuticals USA; 2009 Jan.
5. Cefdinir powder for suspension [package insert]. Sellersville (PA): Teva Pharmaceuticals USA; 2009 Jun.
6. Spectracef® tablets [package insert]. Cary (NC): Cornerstone Therapeutics Inc.; 2009.
7. Cefditoren tablets [package insert]. Cary (NC): Aristos Pharmaceuticals, Inc.; 2009 Jul.
8. Suprax® [package insert]. Baltimore (MD): Lupin Pharmaceuticals Inc.; 2008 Oct.
9. Cefpodoxime tablets [package insert]. Dayton (NJ): Aurobindo Pharma USA, Inc.; 2008 Feb.
10. Cefpodoxime granule for suspension [package insert]. Princeton (NJ): Sandoz Inc.; 2008 Sept.
11. Cedax® [package insert]. Gonzales (LA): Pernix Therapeutics, LLC; 2010 Apr.
12. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2011 [cited 2012 Jul 31]. Available from: http://www.thomsonhc.com/.
13. Phillips H, Van Hook CJ, Butler T, et al. A comparison of cefpodoxime proxetil and cefaclor in the treatment of acute exacerbation of COPD in adults. Chest. 1993;104(5):1387-91.
14. Chirurgi VA, Edelstein H, Oster SE, et al. Ceftibuten versus cefaclor for the treatment of bronchitis. J Antimicrob Chemother. 1991;28:577-80.
15. Fogarty CM, Bettis RB, Griffin TJ, Keyserling CH, Nemeth MA, Tack KJ. Comparison of a 5 day regimen of cefdinir with a 10 day regimen of cefprozil for treatment of acute exacerbation of chronic bronchitis. J Antimicrob Chemother. 2000;45:851-8.
16. Van Herwaarden C, Langan C, Siemon G, Rudolph C, Keyserling C, Nemeth M, et al. International study comparing cefdinir and cefuroxime axetil in the treatment of patients with acute exacerbation of chronic bronchitis. Int J Infect Dis. 1999;4:26-33.
17. Alvarez-Sala JL, Kardos P, Martínez-Beltrán J, Coronel P, Aguilar L. Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. Antimicrob Agents Chemothera. 2006;50(5):1762-7.
18. Zuck P, Petitpretz P, Geslin P, Rio Y, Leblanc F. Bacteriological eradication of streptococcus pneumoniae from patients with acute exacerbations of chronic bronchitis: cefuroxime axetil versus cefixime. Int J Clin Prac. 1999;53(6):437-43.
19. Verghese A, Roberson D, Kalbfleisch JH, Sarubbi F. Randomized comparative study of cefixime versus cephalexin in acute bacterial exacerbations of chronic bronchitis. Antimicrob Agents Chemother. 1990;34(6):1041-4.
20. Handsfield H, McCormack W, Hook E, Douglas J, Covino J, Verdon M, et al. A comparison of single-dose cefixime with ceftriaxone as a treatment for uncomplicated gonorrhea. NEJM. 1991;325(19):1337-41.
21. Verdon M, Douglas J, Wiggins S, Handfield H. Treatment of uncomplicated gonorrhea with single doses of 200 mg cefixime. Sexually Transmitted Diseases. 1993;20(5):290-3.
22. Plourde P, Tyndall M, Agoki E, Ombette J, Slaney L, D'Costa L, et al. Single-dose cefixime versus single-dose ceftriaxone in the treatment of antimicrobial resistant Neisseria gonorrhoeae infection. Journal of Infectious Diseases. 1992;166(4):919-22.
23. Portilla I, Lutz B, Montalvo M, Mogabag W. Oral cefixime versus intramuscular ceftriaxone in patients with uncomplicated gonococcal infections. Sexually Transmitted Diseases. 1992;19(2):94-8.
24. Novak E, Paxton L, Tubbs H, Turner L, Keck C, Yatsu J. Orally administered cefpodoxime proxetil for treatment of uncomplicated gonococcal urethritis in males: a dose-response study. Antimicrobial agents and Chemotherapy. 1992;1764-5.

25. Asmar BI, Dajani AS, Del Beccaro MA, Mendelman PM. Comparison of cefpodoxime proxetil and cefixime in the treatment of acute otitis media in infants and children. Pediatrics. 1994;94(6):847-52.
26. Nemeth M, McCarty J, Gooch H, Henry D, Keyserling C, Tack K. Comparison of cefdinir and penicillin for the treatment of streptococcal pharyngitis. Clinical Therapeutics. 1999;21(11):1873-81.
27. Tack K, Henry D, Gooch W, Brink D, Keyserling C and the Cefdinir Pharyngitis Study Group. Five-day cefdinir treatment for streptococcal pharyngitis. Antimicrobial Agents and Chemotherapy. 1998;42(5):1073-5.
28. Brook I. A pooled comparison of cefdinir and penicillin in the treatment of group A beta-hemolytic streptococcal pharyngotonsillitis. Clin Therap. 2005;27(8):1266-73.
29. Ozaki T, Nishimura N, Suzuki M, Narita A, Watanabe N, Ahn J, et al. Five-day oral cefditoren pivoxil versus 10-day oral amoxicillin for pediatric group A streptococcal pharyngotonsillitis. J Infect Chemother. 2008;14:213-8.
30. Block S, Hedrick J, Tyler R. Comparative study of the effectiveness of cefixime and penicillin V for the treatment of streptococcal pharyngitis in children and adolescents. Pediatr Infect Dis J. 1992;11:919-25.
31. Adam D, Cefixime Study Group, Hostalek U, Troster K. 5-day cefixime therapy for bacterial pharyngitis and/or tonsillitis: comparison with 10-day penicillin V therapy. Infection. 1995;23(Suppl 2):S83-6.
32. Pichichero ME, Gooch WM, Rodriguez W, Blumer JL, Aronoff SC, Jacobs RF, et al. Effective short-course treatment of acute group A beta-hemolytic streptococcal tonsillopharyngitis. Arch Pediatr Adolesc Med. 1994;148:1053-60.
33. Pichichero M, McLinn S, Gooch M, Rodriguez M, Goldfarb J, Reidenberg B, et al. Ceftibuten vs. penicillin V in group A beta-hemolytic streptococcal pharyngitis. Pediatr Infect Dis J. 1995;14:S102-7.
34. van Zyle L, le Roux J, LaFata J, Volk R, Palo W, Flamm R, et al. Cefditoren pivoxil versus cefpodoxime proxetil for community-acquired pneumonia: results from a multi-center, prospective, randomized, double-blind study. Clin Therap. 2002;24(11):1840-53.
35. Drehobl M, Bianchi P, Keyserling CH, Tack KJ, Griffin TJ. Comparison of cefdinir and cefaclor in the treatment of community-acquired pneumonia. Antimicrob Agents Chemother. 1997;41(7):1579-83.
36. Sengupta J, Mondal AK, Jain P, Garg RD, Mathur NC, Moharana AK. Comparative evaluations of cefpodoxime versus cefixime in children with lower respiratory tract infections. Indian J Pediatr. 2004;71(6):517-21.
37. Tack KJ, Keyserling CH, McCarty J, Hedrick JA. Study of use of cefdinir versus cephalexin for treatment of skin infections in pediatric patients. Antimicrob Agents and Chemother. 1997;41(4):739-42.
38. Tack K, Littlejohn T, Mailloux G, Wolf M, Keyserling C. Cefdinir versus cephalexin for the treatment of skin and skin structure infections. Clin Therap. 1998;20(2):244-56.
39. Stevens DL, Pien F, Drehobol M. Comparison of oral cefpodoxime proxetil and cefaclor in the treatment of skin and soft tissue infections. Diagn Microbiol Infect Dis. 1993;16:123-9.
40. Bucko AD, Hunt BJ, Kidd SL, Hom R. Randomized, double-blind, multicenter comparison of oral cefditoren 200 or 400 mg BID with either cefuroxime 250 mg BID or cefadroxil 500 mg BID for the treatment of uncomplicated skin and skin-structure infections. Clin Ther. 2002;27(7):1134-47.
41. Gehanno P, Depondt J, Barry B, Simonet M, Dewever H. Comparison of cefpodoxime proxetil with cefaclor in the treatment of sinusitis. J Antimicrob Chemother. 1990;26(Suppl E): 87-91.
42. Leigh AP, Nemeth MA, Keyserling CH, Hotary LH, Tack KJ. Cefdinir versus cefaclor in the treatment of uncomplicated urinary tract infection. Clin Ther. 2000;22(7):818-25.
43. Ho MW, Wang FD, Fung CP, Liu CY. Comparative study of ceftibuten and cefixime in the treatment of complicated urinary tract infections. J Microbiol Immunol Infect. 2001;34:185-9.
44. Ziering W, McElvaine P. Randomized comparison of once-daily ceftibuten and twice daily clarithromycin in the treatment of acute exacerbations of chronic bronchitis. Infection 1998;26(1):68-75.
45. Martin DH, Sargent SJ, Wendel GD Jr, McCormack WM, Spier NA, Johnson RB. Comparison of azithromycin and ceftriaxone for the treatment of chancroid. Clin Infect Dis. 1995;21:409-14.
46. French LM, Smaill FM. Antibiotic regimens for endometritis after delivery. Cochrane Database Syst Rev. 2004;18(4):CD001067.
47. Piippo T, Stefansson S, Pitkäjärvi T, Lundberg C. Double-blind comparison of cefixime and cefaclor in the treatment of acute otitis media in children. Scand J Infect Dis. 1991;23:459-65.
48. MacLoughlin GJ, Barreto DG, de la Torre C, Pinetta EA, del Castillo F, Palma L. Cefpodoxime proxetil suspension compared with cefaclor suspension for treatment of acute otitis media in pediatric patients. J Antimicrob Chemother. 1996;37:565-73.
49. Blumer JL, McLinn SE, Deabate A, et al. Multinational multicenter controlled trial comparing ceftibuten with cefaclor for the treatment of acute otitis media. Pediatr Infect Dis J. 1995;14:S115-20.
50. Blumer JL, Mclinn SE, Deabate CA, Kafetzis DA, Perrotta RJ, Salgado O. Five-day cefdinir course vs ten-day cefprozil course for treatment of acute otitis media. Pediatr Infect Dis J. 2000;19(12):S147-S52.
51. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
52. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest. 2005 May;127(5):1752-63.
53. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004 May;113(5):1451-65.
54. American Academy of Pediatrics. Clinical practice guidelines: management of sinusitis. Pediatrics. 2001;108(3):798-808.
55. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR Morb Mortal Wkly Rep. 2010;59(No. RR-12):1-116. Available from: http://www.cdc.gov/std/treatment/2010/. Accessed June 14, 2011.
56. Rodriguez-Roisin R, Anzueto A, Bourbeau J, deGuia T, Hui D, Jenkins C, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2010). [guideline on the internet]. Global Initiative for

Chronic Obstructive Lung Disease, Inc.; 2010 [cited 2012 Jul 31]. Available from: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html.

Therapeutic Class Review
Third Generation Cephalosporins

Overview/Summary

The cephalosporin family of antibiotics is part of a larger group known as β-lactam antibiotics. Agents within this group share the structural feature of a β-lactam ring. The β-lactam antibiotics are generally considered bactericidal and work by inactivating enzymes involved with bacterial cell wall synthesis.[1] Cephalosporins cover a wide range of organisms and are frequently used antibacterial agents due to their spectrum of activity and ease of administration.[2]

Cephalosporins are grouped into generations, based on their spectrum of activity. The first generation cephalosporins are active against gram-positive aerobes but are inactive against penicillin-resistant pneumococci. They typically have poor activity against gram-negative organisms, though some strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Shigella* may be susceptible. Second generation cephalosporins have greater activity against *Haemophilus influenza* compared to the first generation cephalosporins and have enhanced activity against gram-negative bacteria in vitro. Third generation cephalosporins are active against streptococci, *Haemophilus influenza* and *Moraxella catarrhalis* and are more active against gram-negative bacilli compared to first or second generation cephalosporins; however, they are not as active against susceptible strains of staphylococci compared to first generation cephalosporins. Among the orally available third generation cephalosporins, cefpodoxime proxetil and cefdinir have more activity against staphylococci compared to cefixime and ceftibuten, while ceftibuten is weakly active against pneumococci. Its spectrum of activity is similar to cefdinir and cefpodoxime.[2,3] Fourth generation cephalosporins have enhanced activity against gram-negative bacteria compared to the first and second generation cephalosporins and have activity in vitro against gram-negative bacteria that are typically resistant to the third generation cephalosporins, including *Pseudomonas aeruginosa* and Enterobacteriaceae. In addition, they may be more active against gram-positive bacteria compared to some third generation cephalosporins. The only fourth generation cephalosporin is cefepime, which is only available parenterally. As a family, cephalosporins have poor activity against enterococci, Listeria and oxacillin-resistant staphylococci.[2,3]

Collectively, the cephalosporins are able to reach therapeutic levels in urine and in pleural, pericardial, peritoneal and synovial fluid. With the exception of cefuroxime, the first and second generation cephalosporins are not able to effectively penetrate the cerebrospinal fluid and therefore should not be used to treat central nervous system infections. Conversely, the third generation cephalosporins do effectively penetrate the cerebrospinal fluid.[2]

This review will focus on the oral third generation cephalosporins. Currently cefixime (Suprax®) and ceftibuten (Cedax®) are only available as branded agents. All other third generation cephalosporins are available generically in at least one dosage form or strength.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Cefdinir*	Third generation cephalosporin	a
Cefditoren (Spectracef®*)	Third generation cephalosporin	a
Cefixime (Suprax®)	Third generation cephalosporin	-
Cefpodoxime*	Third generation cephalosporin	a
Ceftibuten (Cedax®)	Third generation cephalosporin	-

*Generic available in at least one dosage form or strength.

The third generation cephalosporins have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for the third generation cephalosporins that are noted in Table 3. The third generation cephalosporins may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Third Generation Cephalosporins[4-11]

Bacteria	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Gram-Positive Aerobes					
Staphylococcus aureus	a *	a *		a *	
Staphylococcus saprophyticus				a	
Streptococcus pneumoniae	a †	a †	a ‡	a †	a †
Streptococcus pyogenes	a	a	a	a	a
Gram-Negative Aerobes					
Escherichia coli			a	a	
Haemophilus influenzae	a *	a *	a *	a *§	a *
Haemophilus parainfluenzae	a *	a *			
Klebsiella spp.				a	
Moraxella (Branhamella) catarrhalis	a *	a *	a *	a *	a *
Neisseria gonorrhoeae			a ‖	a ‖	
Proteus mirabilis			a	a	

*Including β-lactamse producing strains.
†Penicillin-susceptible strains only.
‡β-lactamse positive and negative strains.
§Only non-β-lactamse producing strains for the treatment of acute bacterial exacerbations of chronic bronchitis.
‖Including penicillinase-producing strains.

Indications

Table 3. Food and Drug Administration (FDA)-Approved Indications[4-11]

Indication	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Dermatologic					
Skin and skin structure infections	a	a		a	
Genitourinary					
Acute ano-rectal infections in women				a	
Gonorrhea, uncomplicated			a	a	
Urinary tract infections			a	a	
Respiratory					
Acute bacterial exacerbations of chronic bronchitis	a	a	a	a	a
Acute maxillary sinusitis	a			a	
Community-acquired pneumonia	a	a		a	
Otitis media	a		a	a	a
Pharyngitis and/or tonsillitis	a	a	a	a	a
Acute bronchitis			a		

Pharmacokinetics

Table 4. Pharmacokinetics[4-12]

Generic Name	Time to Peak Blood Levels (hours)	Protein Binding (%)	Renal Excretion (%)	Serum Half-Life (hours)
Cefdinir	2 to 4	60 to 70	11.6 to 18.4	1.7
Cefditoren	1.5 to 3.0	88	16 to 22	1.6
Cefixime	2 to 6	65	50	3 to 9
Cefpodoxime	2 to 3	21 to 29	29 to 33	2.0 to 2.8
Ceftibuten	2.0 to 2.6	65	56	2.0 to 2.4

Clinical Trials

The clinical studies demonstrating the safety and efficacy of the third generation cephalosporins in their respective Food and Drug Administration-approved indications are listed in Table 5.[13-57]

Studies evaluating the third generation cephalosporins for the treatment of acute exacerbations of chronic bronchitis did not consistently demonstrate significant differences in clinical response or eradication rate when compared to other cephalosporin agents.[13-18] Verghese and colleagues compared cefixime and cephalexin in the treatment of hospitalized patients with exacerbations of chronic bronchitis and demonstrated significantly better clinical cure rates in patients treated with cefixime compared to cephalexin (70.8 vs 50.0%; $P<0.05$). The incidence of diarrhea was higher in the cefixime group.[19] In the treatment of gonorrhea, cefixime and cefpodoxime have generally demonstrated comparable efficacy in the rate of bacteriologic cure (>90%) in open-label and dose-response studies, while cefixime has been shown to have comparable efficacy when compared to ceftriaxone.[20-24]

Asmar et al compared cefixime and cefpodoxime in the treatment of acute otitis media. By day 15, the a bacteriologic cure was reported in 83 and 81% of patients treated with cefpodoxime and cefixime, respectively ($P=0.541$).[25] Other head-to-head studies of the third generation cephalosporins in the treatment of acute otitis media demonstrated no statistically significant differences in efficacy between the agents. [47-50] Studies evaluating the use of the third generation cephalosporins for the treatment of pharyngitis and/or tonsillitis have failed to consistently demonstrate “superiority” of any third generation cephalosporins over penicillin or amoxicillin.[26-33] In the treatment of lower respiratory tract infections including community-acquired pneumonia, no cephalosporin consistently demonstrated significant differences when the third generation cephalosporins were compared with each other or with cephalosporins in other generations.[34-36]

Studies evaluating the treatment of skin and soft tissue infections, sinusitis and urinary tract infections did not consistently demonstrate the “superiority” of any third generation cephalosporins when compared with in-class or with other cephalosporins in other generations.[37-43]

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acute Bacterial Exacerbations of Chronic Bronchitis and Secondary Bacterial Infections of Acute Bronchitis				
Phillips et al[13] Cefaclor 250 mg TID vs cefpodoxime 200 mg BID	DB, MC, RCT Patients with signs and symptoms of acute bacterial exacerbation of COPD	N=301 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: There were no statistically significant differences between cefpodoxime and cefaclor in the eradication of the original pathogen (91 vs 92%, respectively; no *P* value reported) or in clinical response at three to seven days post-treatment (99 vs 92%, respectively; *P* value not reported). More bacterial isolates were susceptible to cefpodoxime compared to cefaclor (91 vs 84%, respectively; *P*<0.001). Secondary: There were no statistically significant differences between cefpodoxime and cefaclor in adverse events (11 vs 12%, respectively; *P* value not reported).
Chirurgi et al[14] Cefaclor 250 mg every 8 hours vs ceftibuten 400 mg QD	PRO, RCT Patients with acute bronchitis, not pneumonia	N=45 Unspecified (from 7 to 14 days)	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87.5 and 92.3% of patients treated with ceftibuten and cefaclor, respectively (*P* value not reported). Bacteriologic efficacy was reported as 87.5 and 80.0% of patients treated with ceftibuten and cefaclor, respectively (*P* value not reported). Secondary: The rates of adverse events were reported as 7.9 and 5.6% in patients treated with ceftibuten and cefaclor, respectively (*P* value not reported).
Fogarty et al[15] Cefprozil 500 mg BID (for 10 days) vs cefdinir 300 m BID (for 5 days)	DB, MC, PRO, RCT Patients with acute exacerbations of chronic bronchitis	N=281 5 to 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: Seven to eleven days after the patient had stopped therapy, clinical cure rates were reported as 80 and 72% for patients treated with cefdinir and cefprozil, respectively (*P* value not reported). Seven to eleven days after the patient had stopped therapy, microbiological eradication rates were reported as 81 and 84% for patients treated with cefdinir and cefprozil, respectively (*P* value not reported). Secondary: Patients treated with cefdinir experienced more cases of mild diarrhea than patients treated with cefprozil (17 vs 6%, respectively; *P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Van Herwaarden et al[16] Cefdinir 600 mg QD vs cefdinir 300 mg BID vs cefuroxime 250 mg BID	DB, MC, PG, RCT Patients 13 years of age and older with a history of chronic bronchitis and a current diagnosis of an acute exacerbation of chronic bronchitis	N=1,045 Up to 35 days post-treatment	Primary: Clinical response rate, microbiological eradication Secondary: Appearance of new pathogens during or after treatment	Primary: The clinical response rates for the cefdinir QD, cefdinir BID and cefuroxime groups were 81, 74 and 80%, respectively. No significant difference between groups was observed in clinical response rates (*P* values not reported). Microbiological cure rates at test-of-cure assessment (seven to 14 days post-treatment) were 90% in the cefdinir QD group, 85% in the cefdinir BID group, and 88% in the cefuroxime group. The cefdinir QD and BID groups were comparable to the cefuroxime group in microbiological cure rates at test-of-cure assessment but the cefdinir QD group was slightly more effective than the BID group (*P* values not reported). At the long-term follow-up assessment (21 to 35 days post-treatment), the microbiological eradication rates were 95% for cefdinir QD, 99% for cefdinir BID and 99% for cefuroxime (*P* values not reported). The corresponding values for clinical response rates were 93, 95 and 93%, respectively (*P* values not reported). Secondary: Thirty-two patients in the cefdinir QD group, 45 patients in the cefdinir BID group and 39 patients in the cefuroxime group developed a respiratory tract superinfection during the study (*P* values not reported). Eleven patients were reinfected with pathogens not present at baseline after the test-of-cure assessment (three patients in the cefdinir QD group, six patients in the cefdinir BID group and two patients in the cefuroxime group; *P* values not reported).
Alvarez-Sala et al[17] Cefuroxime 250 mg BID (for 10 days) vs	DB, DD, PG, RCT Patients 18 years of age and older with acute	N=541 5 to 10 days	Primary: Clinical evaluation, bacteriologic evaluation Secondary: Adverse events	Primary: On day 11, clinical success rate was reported as 79.9 and 82.7% for patients treated with cefditoren and cefuroxime, respectively (*P*=NS). On day 30, clinical success rate was reported as 81.0% and 85.5% for patients treated with cefditoren and cefuroxime, respectively (*P*=NS). On day 11, bacteriological response was reported as 72.8 and 67.0% for patients treated with cefditoren and cefuroxime, respectively (*P*=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cefditoren 200 mg BID (for 5 days)	exacerbations of chronic bronchitis			Secondary: Drug-related adverse events were reported in 7.7 and 11.4% of patients treated with cefditoren and cefuroxime, respectively (*P* value not reported).
Zuck et al[18] Cefuroxime 250 mg by mouth BID vs cefixime 200 mg BID	DB, MC, PG, RCT Hospitalized patients 30 to 75 years of age experiencing acute exacer-bations of chronic bronchitis	N=58 8 days	Primary: Clinical cure, microbiological eradication Secondary: Adverse events	Primary: At two to four days post-treatment, clinical cure was reported in 94 and 71% of patients treated with cefuroxime and cefixime, respectively (*P*=NS); microbiological eradication occurred more quickly in patients treated with cefuroxime compared to patients treated with cefixime (*P*=0.002 at two to four weeks post-treatment). Secondary: Both treatments were well tolerated. One patient treated with cefuroxime reported fever; one patient treated with cefixime reported buccal mycosis.
Verghese et al[19] Cephalexin 250 mg QID vs cefixime 400 mg for 1 dose	RCT Patients with purulent exacerbation of chronic bronchitis	N=86 1 to 14 days	Primary: Clinical cure, clinical improvement Secondary: Adverse events	Primary: Clinical cure was reported as 70.8 and 50.0% in patients treated with cefixime and cephalexin, respectively (*P*<0.05). Combined percentages for clinical cure and improvement were reported as 95.8 and 84.2% in patients treated with cefixime and cephalexin, respectively (*P*=0.06). Secondary: Both treatments were well tolerated. Diarrhea occurred more often in patients treated with cefixime compared to patients treated with cephalexin (*P*=0.013).
Ziering et al[44] Ceftibuten 400 mg QD vs clarithromycin 500 mg BID	DB, MC, PG Patients 18 years of age and older with acute exacerbations of chronic bronchitis	N=309 7 to 14 days	Primary: Clinical assessment, microbiological assessment, overall success rate Secondary: Adverse events	Primary: At the end of the treatment, clinical success was reported in 91 and 93% of patients treated with ceftibuten and clarithromycin, respectively. At seven to 21 days post-treatment, clinical cure was reported as 92.6 and 93.3%, of patients treated with ceftibuten and clarithromycin, respectively. Overall success rate was reported as 84.3 and 86.7%, of patients treated with ceftibuten and clarithromycin, respectively (*P*=NS). At the end of the treatment, microbiological eradication rates were reported in 84.8 and 89.5%, of patients treated with ceftibuten and clarithromycin, respectively. At seven to 21 days post-treatment, microbiological eradication was reported as 100% in both treatment groups (*P*=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Less patients treated with ceftibuten compared to clarithromycin reported drug-related adverse events (5.3 vs 21.9%, respectively; *P*<0.001) likely due to taste perversion associated with clarithromycin intake (*P*<0.001).
Chancroid				
Martin et al[45] Azithromycin 1 g as a single dose vs ceftriaxone 250 mg intramuscularly as a single dose	MC, RCT Patients 16 years of age and older with the presence of a painful genital ulcer, negative darkfield examination, and a negative syphilis reagent test (unless the patient had a previous history of syphilis)	N=197 19 to 23 days	Primary: Response to treatment Secondary: Not reported	Primary: Complete healing was documented in 66% of azithromycin patients and 52% of ceftriaxone patients at the first visit (six to eight days after treatment; *P*>0.05). By the third follow-up visit, 100% of patients in the azithromycin group were completely healed compared to 88% of patients in the ceftriaxone group (*P*>0.05). The remaining four patients in the ceftriaxone group at visit three were judged as clinically improved. Secondary: Not reported
Female Pelvic and Genital Tract Infections				
French et al[46] Clindamycin plus an aminoglycoside vs various alternative antibacterial regimens	MA Women with postpartum endometritis, after cesarean section or vaginal birth	N=1,902 Precise duration of therapy not specified	Primary: Treatment failure Secondary: Not reported	Primary: Nineteen studies comparing clindamycin plus an aminoglycoside (usually gentamicin) with an alternative regimen demonstrated more treatment failures with the other regimen (RR, 1.44; 95% CI, 1.15 to 1.8). The overall failure rate of clindamycin plus gentamicin was 11.4% (106/928). The incidence of diarrhea was more common with the clindamycin regimens, though not at a statistically significant level (95% CI, 0.35 to 1.25). Seven studies (N=741) compared a second or third generation cephalosporin with another regimen (usually clindamycin plus gentamicin) and demonstrated no difference in treatment failures between groups (RR,1.39; 95% CI, 0.90 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				2.15). The incidence of diarrhea was less frequent with the cephalosporin group. Four trials (N=603) compared aztreonam plus clindamycin with other regimens (i.e., clindamycin plus gentamicin or trospectomycin) and did not reveal evidence of a difference between groups. One trial (N=97) investigated the difference between ciprofloxacin and clindamycin plus gentamicin and demonstrated more treatment failures in the ciprofloxacin group, though not at a statistically significant level (RR,1.96; 95% CI, 0.20 to 4.21). Secondary: Not reported
Gonorrhea				
Handsfield et al[20] Cefixime 400 mg as a single dose vs cefixime 800 mg as a single dose vs ceftriaxone 250 mg intramuscularly as a single dose	RCT Patients 16 years of age and older with isolation of *N gonorrhoeae* at enrollment	N=333 3 to 10 days post-treatment	Primary: Cure rates Secondary: Not reported	Primary: Overall cure rates were 96% in the cefixime 400 mg group, 98% in the cefixime 800 mg group and 98% in the ceftriaxone group (*P* values not reported). Secondary: Not reported
Verdon et al[21] Cefixime 200 mg as a single dose	OL, RCT Patients with gonococcal infection	N=125 4 to 7 days post-treatment	Primary: Eradication rates Secondary: Not reported	Primary: Genital and rectal gonorrhea was eradicated in 95% of patients. Treatment was effective in 95% of men with urethral infection and 94% of women with anogenital infection. Two of three pharyngeal infections were eradicated.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Plourde et al[22] Cefixime 400 mg as a single dose vs ceftriaxone 250 mg intramuscularly as a single dose	RCT Patients 18 to 65 years of age with *N gonorrhoeae* infection	N=236 4 to 7 days post-treatment	Primary: Bacteriologic cure Secondary: Not reported	Primary: Bacteriological cure was observed in 98% of cefixime patients and 100% of ceftriaxone patients (*P* value not reported). Secondary: Not reported
Portilla et al[23] Cefixime 400 mg as a single dose vs cefixime 800 mg as a single dose vs ceftriaxone 250 mg intramuscularly as a single dose	RCT Patients 18 to 44 years of age with gonococcal infection	N=187 4 to 9 days post-treatment	Primary: Bacteriologic cure Secondary: Not reported	Primary: Bacteriologic eradication was observed in 97% of cefixime patients and 100% of ceftriaxone patients. Secondary: Not reported
Novak et al[24] Cefpodoxime 50 mg as a single dose vs cefpodoxime 100 mg as	DR, OL Male patients 18 to 46 years of age with uncomplicated *N gonorrhoeae* infection	N=58 4 to 9 days post-therapy	Primary: Eradication rates Secondary: Not reported	Primary: A 100% eradication rate was observed at all dose groups from 50 to 600 mg. Among patients evaluated, eight β-lactamase positive strains were identified. A dose of 200 mg of cefpodoxime was chosen for phase III studies due to efficacy and pharmacokinetic parameters. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
a single dose vs cefpodoxime 200 mg as a single dose vs cefpodoxime 400 mg as a single dose vs cefpodoxime 600 mg as a single dose Doses started at 600 mg and were reduced when bacteriologic eradication rates were ≥90%. When the eradication rate was ≤80% the dose was not reduced any further and the 10 previous subjects were to be given probenecid 1 g.				Not reported
Otitis Media				
Piippo et al[47] Cefaclor 40 mg/kg/day divided BID vs	DB, PG, RCT Pediatric patients aged 6 months to 12 years with acute otitis media	N=345 7 days	Primary: Clinical cure Secondary: Adverse events	Primary: At days 10 to 12, clinical cure was reported in 93.5 and 90.5% of patients treated with cefixime and cefaclor, respectively (*P*=0.081). At days 28 to 35, clinical cure was reported in 90.1 and 86.6% of patients treated with cefixime and cefaclor, respectively (*P*=0.12). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cefixime 8 mg/kg/day divided BID				Adverse events were reported in 17.9 and 10.6% of patients treated with cefixime and cefaclor, respectively (*P* value not reported).
MacLoughlin et al[48] Cefaclor suspension 40 mg/kg/day divided TID vs cefpodoxime suspension 10 mg/kg/day divided BID	MC, OL, RCT Pediatric patients aged 1 month to 11 years with acute otitis media	N=167 5 days	Primary: Clinical efficacy Secondary: Adverse events	Primary: Clinical success was reported as 93.6 and 91.6% of patients treated with cefpodoxime and cefaclor, respectively (*P*>0.05); at study day 30, clinical recurrence was reported as 99 and 94%, respectively (*P*>0.05). Secondary: Patients were able to tolerate both cefpodoxime and cefaclor (99 vs 94%, respectively; *P*>0.05).
Blumer et al[49] Cefaclor 40 mg/kg/day in 3 divided doses (maximum 1 g/day) vs ceftibuten 9 mg/kg/day for 1 dose (maximum 400 mg/day)	MC, RCT, SB Pediatric patients aged 3 months to 17 years with acute otitis media	N=154 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At one to three days post-treatment, clinical cure was reported in 89 and 88% of patients treated with ceftibuten and cefaclor, respectively (*P*=NS). At two to four weeks post-treatment, clinical cure was reported in 88 and 82% of patients treated with ceftibuten and cefaclor, respectively (*P*=NS). Secondary: Mild to moderate drug-related adverse events were reported in 8 and 14% of patients treated with ceftibuten and cefaclor, respectively (*P* values not reported).
Block et al[50] Cefprozil 30 mg/kg/day divided BID (for 10 days) vs cefdinir 14 mg/kg/day divided BID (for 5 days)	DB, MC, PRO Pediatric patients aged 6 months to 12 years with acute otitis media	N=373 5 to 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At the end of therapy (study days nine to 11), clinical efficacy was reported as 80.0 and 82.5% in patients treated with cefdinir and cefprozil (*P*=NS). Secondary: Diarrhea and overall adverse events were reported in cefdinir-treated patients (7.8 and 13.0%, respectively) and cefprozil-treated patients (4.2 and 12.0%, respectively; *P*=0.116).
Asmar et al[25] Cefixime oral suspension 8 mg/kg/day QD	DB, MC, PRO, RCT Patients aged 2 months to 17	N=368 10 days	Primary: Clinical evaluations, microbiologic evaluations	Primary: On days 12 through 15, clinical cure or improvement was reported in 83 and 81% of patients treated with cefpodoxime and cefixime, respectively (*P*=0.541). On days 12 to 15, end-of-therapy response rates were reported as 53 and 51%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cefpodoxime oral suspension 10 mg/kg/day QD	years with acute suppurative otitis media		Secondary: Adverse events	in patients treated with cefpodoxime and cefixime, respectively (*P*=0.404). Overall microbiologic susceptibility was reported as 89 and 86% in patients treated with cefpodoxime and cefixime, respectively (*P*=0.70). Secondary: Drug-related adverse effects (e.g., diarrhea, diaper rash, vomiting and rash) occurred in 23.3 and 17.9% of patients treated with cefpodoxime and cefixime, respectively (no *P* values reported).
Block et al[51] Azithromycin suspension 10 mg/kg QD on day 1 then 5 mg/kg QD for 4 days vs cefdinir suspension 7 mg/kg every 12 hours for 5 days	MC, PRO, RCT, SB Patients 6 months to 6 years of age with acute otitis media	N=357 25 days	Primary: Clinical response, signs and symptoms of infection Secondary: Parental satisfaction with treatment, adverse events	Primary: Clinical cure rates at the end-of-therapy visit (seven to nine days) were comparable between groups (85% for azithromycin and 87% for cefdinir; 95% CI, -5.5 to 9.8). Comparable clinical cure rates were sustained at the follow-up visit (20 to 25 days) in patients who were cured at the end-of-therapy visit (86% for azithromycin and 76% for cefdinir; 95% CI, -18.9 to 0.0). Clinical cure rates at end-of-therapy were comparable between groups in patients who were previously vaccinated with conjugated heptavalent pneumococcal vaccine (PCV7) 83% for azithromycin and 86% for cefdinir; 95% CI, -6.5 to 11.8). No significant differences were observed between groups in signs and symptoms of infection at the end-of-therapy visit. Secondary: The study drugs were comparable based on parental satisfaction ratings, ease of use, taste, compliance, health care resource utilization and missed work or daycare. Most adverse events were mild or moderate and resolved without need for additional treatment.
Mandel et al[52] Erythromycin/	DB, RCT Patients 7	N=331 12 weeks	Primary: Proportion of patients effusion-	Primary: There were no significant differences in the proportion of patients who were effusion-free in the erythromycin/sulfisoxazole or cefaclor group compared to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sulfisoxazole 50 mg/kg/day of erythromycin component and 150 mg/kg/day of sulfisoxazole component in 4 divided doses vs amoxicillin 40 mg/kg/day in 3 divided doses vs cefaclor 40 mg/kg/day in 3 divided doses vs placebo	months to 12 years of age with otitis media with effusion and without symptoms of acute otitis media (otalgia, fever)		free at two and four weeks in the erythromycin/ sulfisoxazole and cefaclor groups compared to the amoxicillin group Secondary: Recurrence rate of middle ear effusion following antibiotic therapy, speech recognition threshold at two and four weeks	amoxicillin group at week two or four ($P \geq 0.39$). Secondary: There were no significant differences between groups in the recurrence rate of middle ear effusion after antibiotic therapy. Speech recognition threshold was statistically higher in both the right and left ears in the placebo group than in the antimicrobial groups at two weeks ($P \leq 0.04$). At four weeks, this difference was only present in the right ear ($P=0.03$), not in the left ear ($P=0.19$).
Pharyngitis/Tonsillitis				
Nemeth et al[26] Cefdinir 600 mg QD vs cefdinir 300 mg BID vs penicillin V 250 mg QID	DB, MC, RCT Patients 13 years of age and older with erythema and pain of the pharyngeal cavity and a positive rapid streptococcal antigen test	N=919 Up to 24 days post-therapy	Primary: Clinical response, microbiological response Secondary: Tolerability	Primary: At the test-of-cure visit (four to nine days post-treatment), clinical cure rates for the cefdinir QD, cefdinir BID and penicillin groups were 94.8, 96.3 and 88.9% respectively ($P=0.02$ for penicillin compared to cefdinir QD and $P<0.01$ for penicillin compared to cefdinir BID). At the test-of-cure visit (four to nine days post-treatment), microbiological cure rates for the cefdinir QD, cefdinir BID and penicillin groups were 91.4, 91.7 and 83.4% respectively ($P=0.02$ for penicillin compared to cefdinir QD and $P=0.01$ for penicillin compared to cefdinir BID). No significant differences were observed in clinical or microbiological cure rates between cefdinir QD and cefdinir BID groups ($P=0.52$ and $P=0.95$ respectively). At long-term follow-up (17 to 24 days post-treatment), microbiological eradication

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				rates were 94.9, 96.1 and 92.3% respectively for cefdinir QD, cefdinir BID and penicillin (*P* values not reported). At long-term follow-up (17 to 24 days post-treatment), clinical cure rates were 95.6, 98.4 and 92.8% respectively for cefdinir QD, cefdinir BID and penicillin (*P* values not reported). Secondary: Significantly more adverse effects were observed in the cefdinir groups compared to the penicillin group (*P*<0.001).
Tack et al[27] Cefdinir 300 mg BID vs penicillin V 250 mg QID	MC, RCT, SB Patients 13 years of age and older with erythema and pain of the pharyngeal cavity and a positive rapid streptococcal antigen test	N=558 Up to 31 days	Primary: Clinical response, microbiological response Secondary: Not reported	Primary: The clinical cure rates at test-of-cure (five to 10 days post-therapy) were 89.0 and 84.6% in the cefdinir and penicillin groups respectively (95% CI for difference in cure rates, -2.0 to 10.8). The microbiological eradication rates at test-of-cure (five to 10 days post-therapy) were 88.5 and 82.2% in the cefdinir and penicillin groups respectively (95% CI for difference in eradication rates, -0.4 to 12.9). At long-term follow-up, eradication rates were 81.7 and 77.9% for the cefdinir and penicillin groups respectively. Secondary: Not reported
Brook[28] Cefdinir 600 mg (adults) or 14 mg/kg (pediatrics) QD (for 10 days) vs cefdinir 300 mg (adults) or 7 mg/kg (pediatrics) BID (for 5 to 10 days)	4 DB/SB, MC, PC, RCT Patients with throat pain, erythema, and a positive rapid streptococcal screening test; study A and B participants were <13 years	N=2,751 5 to 10 days	Primary: Clinical cure rate, bacterial eradication rate Secondary: Adverse events	Primary: Combined clinical cure rate was reported as higher for patients treated with cefdinir compared to patients treated with penicillin (94 vs 83%, respectively; *P*<0.001). Combined bacterial eradication rate was higher for patients treated with cefdinir compared to patients treated with penicillin (92 vs 77%, respectively; *P*<0.001). Secondary: All treatments were well tolerated; 98% of patients completed the treatment regimens. Patients treated with cefdinir reported diarrhea, nausea, headache, and vaginal moniliasis; patients treated with penicillin reported diarrhea, nausea, headache, and vomiting.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs penicillin 250 mg (adults) or 10 mg/kg (pediatrics) QID (for 10 days) In studies A through D, participants received either cefdinir or penicillin.	of age; study C and D participants were ≥13 years of age			
Ozaki et al[29] Cefditoren 3 mg/kg TID vs amoxicillin 10 mg/kg TID	PRO Pediatric patients with group A streptococcal pharyngitis	N=258 4 weeks	Primary: Eradication rates, recurrence rates Secondary: Not reported	Primary: Eradication was observed in 99% of cefditoren patients and 100% of amoxicillin patients. No significant differences were observed between groups in eradication rates (*P*=0.22). Recurrence occurred in eight and 15 patients in the cefditoren and amoxicillin groups respectively. No significant differences were observed between groups in recurrent rates (*P*=0.61). Secondary: Not reported
Block et al[30] Cefixime 8 mg/kg QD vs penicillin V 250 mg TID	OL, RCT Pediatric patients 4 to 12 years of age with group A β-hemolytic streptococcal pharyngitis	N=110 6 weeks	Primary: Clinical response, bacteriological response Secondary: Not reported	Primary: No significant difference was observed between the cefixime and penicillin groups in clinical cure at the end of treatment (two to seven days post-treatment; *P* value not reported). Significantly more patients in the penicillin group experienced a relapse compared to those in the cefixime group (11 and three respectively; *P*<0.05). At the end of treatment, eradication rates were significantly higher in the cefixime group compared to the penicillin group (94 and 77% respectively; *P*<0.05). Up to six weeks post-therapy, significantly more patients in the penicillin group had positive group A β-hemolytic streptococcus cultures compared to patients in the cefixime group (45 and 21% respectively; *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Adam et al[31] Cefixime 8 mg/kg QD vs penicillin V 20,000 units/kg TID	OL, RCT Pediatric patients 1 to 12 years of age with pharyngitis and/or tonsillitis	N=160 4 weeks post-therapy	Primary: Clinical response, bacteriological response Secondary: Safety and tolerability	Primary: The clinical response rate was 96.0% in the cefixime group and 97.4% in the penicillin group (*P* value not reported). Eradication rates were 82.6 and 88.2% in the cefixime and penicillin group respectively (*P* value not reported). Recurrence at three to four weeks post-therapy was 8.0% in the cefixime group and 10.5% in the penicillin group (*P* value not reported). Secondary: Both medications were well-tolerated. Adverse events were observed in four children (5.0%) in the cefixime group and five patients (6.3%) in the penicillin group (*P* value not reported).
Pichichero et al[32] Cefpodoxime suspension 10 mg/kg/day divided in 2 doses (for 5 days; maximum of 200 mg/day) vs cefpodoxime suspension 10 mg/kg/day as 1 dose (for 10 days; maximum of 200 mg/day) vs penicillin suspension 40 mg/kg/day divided into 3 doses (for 10 days; maximum 1 g/day)	DB, MC, PRO, RCT' Patients aged 2 to 17 years with acute tonsillo-pharyngitis	N=484 5 to 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 96, 94, and 91% for patients treated with cefpodoxime (10 days), cefpodoxime (five days), and penicillin, respectively (*P*=NS). At study days five to 10, bacteriologic eradication rates were reported as 95, 90, and 78% for patients treated with cefpodoxime (10 days), cefpodoxime (five days), and penicillin, respectively (*P*=0.003 and *P*=0.02 for cefpodoxime [10 days] and cefpodoxime [five days] vs penicillin, respectively). By the 32- to 38-day post treatment visit, cumulative bacteriologic failure rate was reported as 17, 19, and 35% for patients treated with cefpodoxime (10 days), cefpodoxime (five days), and penicillin, respectively (*P*=0.001 and *P*=0.005 for cefpodoxime [10 days] and cefpodoxime [five days] vs penicillin, respectively). Secondary: All treatments were well-tolerated. Gastrointestinal symptoms were most commonly reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pichichero et al[33] Ceftibuten 9 mg/kg QD vs penicillin 25 mg/kg/day in 3 divided doses	MC, RCT, SB Patients 3 to 18 years of age with pharyngitis and scarlet fever caused by group A β-hemolytic streptococci	N=617 5 to 7 days post-treatment (primary endpoint) and up to 4 weeks follow-up	Primary: Clinical response, bacteriological response Secondary: Not reported	Primary: Significantly more patients in the ceftibuten group achieved clinical cure or improvement compared to patients in the penicillin group at five to seven days post-treatment (97 and 89% respectively; *P*<0.01). At two to three weeks post-treatment, clinically successful outcomes were comparable between patients in the ceftibuten and penicillin groups (90 and 89% respectively; *P* value not reported). Strains producing scarlet fever responded in a comparable manner to both ceftibuten and penicillin. Significantly more patients in the ceftibuten group achieved bacteriologic elimination compared to patients in the penicillin group at five to seven days post-treatment (91 and 80% respectively; *P*<0.01). Higher bacteriological eradication rates were observed in ceftibuten patients with pharyngitis (91%) or scarlet fever (90%) compared to penicillin patients with pharyngitis (80%) or scarlet fever (71%) (*P* values not reported). At two to three weeks post-treatment, no significant differences were observed between the ceftibuten and penicillin groups in bacteriological eradication rates (89 and 79% respectively; *P* value not reported). Secondary: Not reported
Pneumonia/Lower Respiratory Tract Infections				
van Zyle L et al[34] Cefditoren 200 mg BID vs cefditoren 400 mg BID vs	DB, MC, PRO, RCT Patients 12 years of age and older with community-acquired pneumonia	N=851 7 to 14 days post-treatment	Primary: Clinical response, microbiological response Secondary: Not reported	Primary: Clinical cure rates were similar between groups at both the post-treatment (48 hours post-treatment) and follow-up visits (seven to 14 days post-treatment). The overall clinical cure rates for cefditoren 200 mg, cefditoren 400 mg and cefpodoxime were 90.5, 89.7 and 92.2% respectively at the post-treatment visit and 88.4, 87.2 and 90.4% respectively at the follow-up visit (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cefpodoxime 200 mg BID				At the post-treatment visit, the overall eradication rates were 88.7% for cefditoren 200 mg, 89.9% for cefditoren 400 mg and 95.7% for cefpodoxime. A significantly better eradication rate was observed for cefpodoxime compared to cefditoren 200 mg (*P*=0.031). At the follow-up visit, the overall eradication rates were 80.0% for cefditoren 200 mg, 85.7% for cefditoren 400 mg and 91.7% for cefpodoxime. A significantly better eradication rate was observed for cefpodoxime compared to cefditoren 200 mg (*P*=0.005). Secondary: Not reported
Drehobl et al[35] Cefaclor 500 mg TID vs cefdinir 300 mg BID	DB, MC, RCT Patients with community-acquired pneumonia	N=538 10 days	Primary: Clinical response, microbiological eradication Secondary: Adverse events	Primary: Satisfactory clinical response was reported as 89 and 86% of patients treated with cefdinir and cefaclor, respectively; microbiological eradication was reported as 92 and 93%, respectively (*P*=NS). Secondary: Patients treated with cefdinir reported a higher incidence of diarrhea compared to patients treated with cefaclor (13.7 vs 5.3%, respectively; *P*<0.001).
Sengupta et al[36] Cefixime 4 mg/kg BID vs cefpodoxime 5 mg/kg BID	AC, MC, OL, PRO, RCT Pediatric patients aged 6 months to 12 years with community-acquired lower respiratory tract infections, including community-acquired pneumonia and acute	N=776 10 to 14 days	Primary: Clinical cure, bacteriologic eradication Secondary: Adverse events	Primary: Clinical cure was reported as 97.0 and 86.8% for patients treated with cefpodoxime and cefixime, respectively; bacteriologic eradication was reported as 93.4 and 82.9%, respectively (no *P* values were reported). Secondary: Both treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	exacerbations of chronic bronchitis			
Skin and Soft Tissue Infections				
Tack et al[37] Cephalexin 10 mg/kg QID vs cefdinir 7 mg/kg BID	DB, MC, RCT Patients 6 months to 12 years of age diagnosed with an uncomplicated mild to moderate skin or skin-structure infection warranting systemic anti-microbial therapy and/or drainage	N=231 10 days	Primary: Clinical cure rate, microbiologic eradication rate Secondary: Adverse events	Primary: Clinical cure rates were reported as 98.3 and 93.8% in patients treated with cefdinir and cephalexin, respectively (*P*=0.056). Microbiologic eradication rates were reported as 99.4 and 97.4% in patients treated with cefdinir and cephalexin, respectively (*P*=0.14). Secondary: Drug-related adverse events were reported in 16 and 11% of patients treated with cefdinir and cephalexin, respectively (*P*=0.11). The most common side effect was diarrhea.
Tack et al[38] Cephalexin 500 mg QID for 10 days vs cefdinir 300 mg BID for 10 days	DB, MC, RCT Patients 13 years of age and older with acute skin and skin structure infections	N=382 7 to 16 days post-therapy	Primary: Pathogen eradication rate, clinical success rate Secondary: Not reported	Primary: No significant difference was observed between groups in pathogen eradication rate (93% for cefdinir and 89% for cephalexin; *P*=0.105). No significant difference was observed in the rate of superinfection between groups (*P*=0.22). No significant differences between groups was observed in clinical success rates (88% for cefdinir and 87% for cephalexin; *P*=0.617). Secondary: Not reported
Stevens et al[39] Cefaclor 500 mg TID	DB, MC, PC, RCT	N=371 7 to 10 days	Primary: Clinical efficacy and safety	Primary: High pathogen eradication rates were observed for patients treated with either cefaclor or cefpodoxime (98 vs 99%, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cefpodoxime 400 mg BID vs placebo BID to TID	Patients 12 years of age and older with acute single-site skin or skin-structure infections		Secondary; Not reported	Patients with infected wounds responded better to cefpodoxime compared to cefaclor (100 vs 83%, respectively; *P* value not reported). Patients treated with cefaclor reported a higher failure rate compared to patients treated with cefpodoxime (4 vs 1%, respectively; *P*=NS). Both active drug regimens were well tolerated. Secondary: Not reported
Bucko et al[40] Cefadroxil 500 mg BID vs cefditoren 200 mg BID vs cefditoren 400 mg BID vs cefuroxime 250 mg BID In study A, participants received cefditoren 200 mg or cefuroxime; in study B, participants received cefditoren 400 mg or cefadroxil.	MA (2 DB, MC, PG) Patients with uncomplicated skin and skin structure infections	N=1,685 10 days	Primary: Clinical evaluation, microbiologic evaluation Secondary: Adverse events	Primary: Clinical cure rates were reported as 85, 83, 88 and 85% for patients treated with cefditoren 200 mg, cefditoren 400 mg, cefuroxime, and cefadroxil, respectively (no *P* values reported). At seven to 14 days after treatment completion, eradication rates were higher in patients treated with cefuroxime compared to patients treated with cefditoren 200 mg in study one (*P*=0.043). At seven to 14 days after treatment completion, eradication rates were higher for cefditoren 400 mg compared to patients treated with cefadroxil in study two (*P*=0.018). Secondary: A higher rate of drug-related adverse events were reported for patients treated with cefditoren 400 mg compared to all other treatment groups (*P*<0.05 for each comparison). The most common adverse events were mild cases of diarrhea, nausea, and headache.
Sinusitis				
Gehanno et al[41] Cefaclor 500 mg TID vs	DB, MC, PC, PRO, RCT Adult outpatients with	N=236 Mean days 9.9	Primary: Clinical cure, overall clinical efficacy (cure and improvement),	Primary: At the end of the treatment, clinical cure was reported as 84 and 68% of patients treated with cefpodoxime and cefaclor, respectively (*P*=0.01). Overall clinical efficacy was reported as 95 and 93% of patients treated with cefpodoxime and cefaclor, respectively (*P*=NS). Bacteriological eradication was reported as 95

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cefpodoxime 200 mg BID	acute sinusitis		bacteriological eradication Secondary: Adverse events	and 91% of patients treated with cefpodoxime and cefaclor, respectively (*P*=NS). Secondary: Possible drug-related adverse events were reported in nine and 10 patients treated with cefpodoxime and cefaclor, respectively; *P* value not reported.
Surgical Prophylaxis				
Song et al[53] Cefuroxime plus metronidazole vs gentamicin plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic agents as mono or combination therapy	MA MA of 147 relevant RCTs published between 1984 and 1995	147 trials 12 years	Primary: Rate of surgical wound infections Secondary: Not reported	Primary: There was no significant difference in the rate of surgical wound infections between many different regimens. However, certain regimens appeared to be inadequate (e.g., metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus erythromycin on the day before operation). A single dose administered immediately before the operation (or short-term use) was judged as effective as long-term postoperative antimicrobial prophylaxis (OR, 1.17; 95% CI, 0.90 to 1.53). There is no convincing evidence to suggest that the new-generation cephalosporins are more effective than first generation cephalosporins (OR, 1.07; 95% CI, 0.54 to 2.12). Secondary: Not reported
Urinary Tract Infections				
Leigh et al[42] Cefaclor 250 mg TID	DB, MC, PG, RCT Patients 13	N=383 5 days	Primary: Clinical and microbiologic efficacy	Primary: A greater number of pathogens were resistant to treatment with cefaclor compared to treatment with cefdinir (6.7 vs 3.7%, respectively; *P*<0.003). Isolates of *E coli* were more resistant to treatment with cefaclor compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cefdinir 100 mg BID	years of age and older with uncomplicated urinary tract infections		Secondary: Adverse events	treatment with cefdinir (5.1 vs 2.0%, respectively; *P*<0.007). At five to nine days post treatment, patients treated with cefdinir and cefaclor reported statistically equivalent clinical (91.3 vs 93.0%, respectively; *P*=0.539) and microbiologic (84.7 vs 79.7%, respectively; *P*=0.184) response rates. Secondary: Drug-related side effects were greater in patients treated with cefdinir compared to patients treated with cefaclor (20.2 vs 13.0%, respectively; *P*=0.025).
Ho et al[43] Cefixime 200 mg BID vs ceftibuten 200 mg BID	OL, PRO, RCT Patients 18 years of age and older with complicated urinary tract infections	N=45 10 to 14 days	Primary: Clinical efficacy rate, bacteriological eradication rate Secondary: Adverse events	Primary: There was no statistically significant difference in rates of clinical efficacy (78.3 vs 77.3%; *P*=0.9) and bacteriological eradication (52.2 and 63.6%; *P*=0.08) for patients taking ceftibuten and cefixime, respectively. Secondary: Adverse events were minimal for both treatment groups. Patients treated with ceftibuten reported diarrhea and increased transaminase serum levels; patients treated with cefixime reported skin rash and increased transaminase serum levels.
Zalmanovici Trestioreanu et al[54] Nitrofurantoin vs SMX/TMP vs β-lactams (amoxicillin, cefadroxil, cefpodoxime pivmecillinam*) vs	MA Outpatient women 16 to 65 years of age with uncomplicated UTI defined by the presence of urinary complaints (and the absence of upper UTI signs) and leucocyturia or bacteriuria	N=6,016 ≥3 days	Primary: Short-term symptomatic cure and long-term symptomatic cure Secondary: Short-term bacteriological cure, long-term bacterial cure, proportion of patients that developed resistance ≤8 weeks after treatment period,	Primary: There was no statistically significant difference in short-term and long-term symptomatic cure with any of the treatment comparisons: fluoroquinolones vs SMX/TMP (RR, 1.00; 95% CI, 0.97 to 1.03; *P*=0.89 and RR, 0.99; 95% CI, 0.94 to 1.05), β-lactams vs SMX/TMP (RR, 0.95; 95% CI, 0.81 to 1.39; *P*=0.56 and RR, 1.06; 95% CI, 0.93 to 1.21; *P*=0.40), nitrofurantoin vs β-lactams (RR, 1.19; 95% CI, 0.93 to 1.51 and RR, 0.98; 95% CI, 0.83 to 1.14), fluoroquinolones vs β-lactams (RR, 1.15; 95% CI, 0.99 to 1.32; *P*=0.064 and RR, 1.01; 95% CI, 0.96 to 1.05) and nitrofurantoin vs SMX/TMP (RR, 0.99; 95% CI, 0.95 to 1.04; *P*=0.82 and RR, 1.01; 95% CI, 0.94 to 1.09; *P*=0.81). Secondary: In the ITT population comparing fluoroquinolones and SMX/TMP, there was a significant difference in short-term bacteriologic cure that slightly favored fluoroquinolones (RR, 1.03; 95% CI, 1.00 to 1.07; *P*=0.025). The result was no longer significant when patients with susceptible pathogens were compared (RR, 1.03; 95% CI, 0.98 to 1.07; *P*=0.23). This result was similar for long-term

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nalidixic acid vs fluoroquinolones (amifloxacin*, ciprofloxacin, norfloxacin, ofloxacin)			numbers of days to symptom resolution, days of work-loss, adverse event resulting in discontinuation of therapy, proportion of patients that developed rash, diarrhea, any adverse event or complications	bacteriologic cure comparing fluoroquinolones and SMX/TMP (RR, 1.06; 95% CI, 1.00 to 1.12; *P*=0.046). When comparing fluoroquinolones vs β-lactams, short-term bacteriologic cure was significantly greater in patients treated with fluoroquinolones in the ITT population (RR, 1.22; 95% CI, 1.13 to 1.31; *P*<0.00001) and the patients with susceptible pathogens (RR, 1.20; 95% CI 1.07 to 1.35; *P*=0.0018). There were no significant differences in short-term and long-term bacteriologic cure comparing the other treatment groups. Significantly less patients developed rashes with fluoroquinolones vs SMX/TMP (RR, 0.08; 95% CI, 0.71 to 1.29; *P*=0.0.0035) or β-lactams (RR, 0.10; 95% CI, 0.02 to 0.56; *P*=0.0083) and with nitrofurantoin vs SMX/TMP (RR, 0.17; 95% CI, 0.04 to 0.76; *P*=0.020). There were no significant differences in rashes comparing the other treatment groups. Data either could not be analyzed or was missing for number of days to symptom resolution or days of work loss. There were no significant differences in any of the other secondary outcomes when comparing treatment groups.
Bocquet et al[55] Cefixime 8 mg/kg initially followed by 4 mg/kg BID for 10 days vs ceftriaxone 50 mg/kg IV QD for 4 days followed by cefixime 4 mg/kg BID for 6 days	AC, DB, MC, PRO, RCT Infants and children aged 1 to 36 months who presented to an emergency department with a first febrile UTI (defined as fever of ≥38.5° C) with no alternative source for the fever and positive urinalysis (white	N=171 10 days	Primary: Incidence of renal scarring Secondary: Time to apyrexia, adverse events, serum procalcitonin and vesicoureteral reflux	Primary: In the intent-to-treat population, the incidence of renal scarring was 41% (95% CI, 28.7 to 53.3) for children in the oral cefixime alone treatment group and 44.8% (95% CI, 32.0 to 57.6) in the sequential treatment group (difference, -3.8%; 95% CI, -21.6 to 13.9). In the per-protocol analysis, the frequency of renal scarring was 30.8% (95% CI, 18.3 to 43.3) in the oral cefixime treatment group and 27.3% (95% CI, 14.1 to 40.5) for the sequential treatment group (difference, 3.5%; 95% CI, -14.7 to 21.7). In the per-protocol analysis, the incidence of scarring did not differ in between children younger than one year of age and children one to three years of age. The incidence of scarring also did not differ with respect to gender. In the subgroup of children less than three months of age (N=10), there were no infants with renal scarring in the cefixime oral group and two infants with renal scarring in the sequential treatment group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	cell counts ≥10^5/mL) and gram-negative rods in gram-stained urine			The time to apyrexia was no different between the two treatment groups (median, 24 hours in both groups). Two children did not tolerate cefixime because of vomiting, and treatment was changed to parenteral therapy. One child with apparent sepsis received intravenous ceftriaxone instead of oral cefixime. The mean serum procalcitonin concentration was higher in children with renal scarring than in children without scarring (3.2 vs 1.7 ng/mL; *P*=0.002). Voiding cystography was performed for 152 children, of which 40 were found to have vesicoureteral reflux (26.3%). Renal scarring was similar for children with or without vesicoureteral reflux.
Hooton et al[56] Cefpodoxime 100 mg BID for 3 days vs ciprofloxacin 250 mg BID for 3 days	AC, DB, NI, RCT Women 18 to 55 years of age with acute cystitis (symptoms of dysuria, frequency, and/or urgency) and pyuria (white blood cell count≥8 cells/mm^3), and received antimicrobial treatment and also had a positive urine culture (defined as 102 or more colony-forming	N=300 30 days	Primary: Clinical cure rate at day 30 Secondary: Clinical and microbiological cure at the first follow-up visit and vaginal *E. coli* colonization at each follow-up visit	Primary: The overall clinical cure rate at 30 days was 93% for women treated with ciprofloxacin compared to 82% of the cefpodoxime group (difference, 11%; 95% CI, 3 to 18). Because the upper limit of the 95% confidence interval of the difference exceeded 10%, the results did not meet predefined criteria for noninferiority of cefpodoxime (*P*=0.57). Among women without a UTI in the year prior to enrollment, the 30-day clinical cure rate was 96% for the ciprofloxacin group compared to 83% of women treated with cefpodoxime (difference, 13%; 95% CI, 5 to 21). This difference was not seen among women who reported one or more UTIs in the year before enrollment (84 vs 80%, respectively). Among women infected with strains that were susceptible to the study antibiotics, the overall clinical cure rates were 94% for ciprofloxacin compared to 82% for cefpodoxime (difference, 12%; 95% CI, 4 to 20). Among those infected with strains unsusceptible to the treatment antibiotic, the overall clinical cure rate was 50% in the ciprofloxacin group and 67% for cefpodoxime. Secondary: The clinical cure rate at the first follow- up visit (five days following treatment) was 93% for ciprofloxacin compared to 88% for cefpodoxime (difference, 5%; 95% CI, -1 to 12).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	units/mL of uropathogen).			Among patients with available urine culture data, *E. coli* was the causative organism in 38% of nonresponders to treatment for ciprofloxacin compared to 64% for cefpodoxime. Thirteen of 16 women in the cefpodoxime group with no response to treatment caused by *E. coli* had cefpodoxime-susceptible strains at enrollment and during the recurrent UTI, two women had resistant strains at both enrollment and recurrent UTI and one woman had a resistant strain at enrollment but a susceptible strain during the recurrent UTI. The microbiological cure rate at the first follow-up visit (five days after treatment) was 96% in the ciprofloxacin treatment group compared to 81% of patients who received cefpodoxime (difference, 15%; 95% CI, 8 to 23). Among women infected with strains that were susceptible to the study antibiotic, the microbiological cure rates were 97% for women receiving ciprofloxacin and 81% for women treated with cefpodoxime (difference, 16%; 95% CI, 9 to 24). Vaginal *E. coli* colonization was present at enrollment in 82% of women in both treatment groups. By the first follow-up visit, 16% of the women in the ciprofloxacin group compared to 40% in the cefpodoxime group had vaginal *E. coli* colonization. At the 30-day follow-up visit colonization was reported in 29% of the ciprofloxacin group compared to 40% of the cefpodoxime group. The development of subsequent UTI did not correlate with the presence of vaginal *E coli* colonization at the first follow-up visit.
Miscellaneous				
Falagas et al[57] Linezolid vs glycopeptides (vancomycin and teicoplanin*) or β-lactams	MA Patients with complicated skin and soft tissue infections, Gram-positive infections, uncomplicated	N=6,093 Up to 28 days	Primary: Treatment success, all-cause mortality and adverse effects Secondary: Treatment duration, microbiological assessment and	Primary: For all infections, linezolid had significantly higher treatment success with the ITT patients (OR, 1.23; 95% CI, 1.06 to 1.42; *P* value not reported) and clinically assessed patients (OR, 1.41; 95% CI, 1.11 to 1.81; *P*=0.006) compared to the glycopeptides or β-lactams. When only the blinded RCTs were analyzed, there was no significant difference between the treatments in the ITT patients (OR, 1.14; 95% CI, 0.95 to 1.38; *P* value not reported) and in clinically assessed patients (OR, 1.15; 95% CI, 0.89 to 1.48; *P*=0.29). Additionally, there was no significant difference in treatment success in the clinically assessed patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(amoxicillin/clavulanate, ampicillin/sulbactam, cefadroxil, ceftriaxone, oxacillin, dicloxacillin)	skin and soft tissue infections, nosocomial pneumonia, community-acquired pneumonia or MRSA infections		eradication of Gram-positive cocci	when linezolid was compared to vancomycin alone (OR, 1.44; 95% CI, 0.90 to 2.30) or β-lactams (OR, 11.34; 95% CI, 0.99 to 1.81). For the skin and soft tissue infections in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 1.67; 95% CI, 1.31 to 2.12; *P*<0.0001). For bacteremia in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 2.07; 95% CI, 1.13 to 3.78; *P*=0.02). There was no significant difference between linezolid and glycopeptides or β-lactams for the treatment of pneumonia in the clinically assessed patients (OR, 1.03; 95% CI, 0.75 to 1.42; *P*=0.84). This was similar for the subset of patients with nosocomial pneumonia (OR, 1.05; 95% CI, 0.75 to 1.46; *P* value not reported). There was no significant difference in mortality between linezolid and glycopeptides or β-lactams in the ITT patients (OR, 0.97; 95% CI, 0.79 to 1.19; *P* value not reported). There were more adverse events with linezolid compared to glycopeptides or β-lactams in the ITT patients; although, the difference was not significant (OR, 1.40; 95% CI, 0.95 to 2.06; *P*=0.09). Linezolid was associated with significantly more thrombocytopenia in the ITT patients compared to glycopeptides or β-lactams (OR, 11.75; 95% CI, 3.66 to 37.57; *P*<0.0001). Secondary: For all Gram-positive infections in the microbiologically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 1.34; 95% CI, 1.05 to 1.72; *P*=0.02). Linezolid was associated with higher rates eradication rates for *S aureus* in the microbiologically assessed patients compared to the other antibiotics (OR, 1.81; 95% CI, 1.40 to 2.34; *P*<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no significant differences in eradication rate for MRSA between linezolid and the other antibiotics (OR, 1.69; 95% CI, 0.84 to 3.41; *P*=0.014). There was also no significant difference between linezolid and vancomycin in patients with MRSA pneumonia (OR, 1.26; 95% CI, 0.54 to 2.96; *P* value not reported). There was no significant difference in eradication of enterococci species between linezolid and the other antibiotics (OR, 0.95; 95% CI, 0.33 to 2.73; *P*=0.93).

Drug regimen abbreviations: BID=twice daily, QD=daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active controlled, CI=confidence interval, DB=double blind, DD=double-dummy, DR=dose-response, ITT=intent-to-treat, MA=meta analysis, MC=multi-center, NS=non-significant, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PRO=prospective, SB=single blinded, RCT=randomized controlled trial
Miscellaneous abbreviations: COPD=chronic obstructive pulmonary disease, MRSA=methicillin-resistant *Staphylococcus aureus*

Special Populations

Table 6. Special Populations[4-11]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Cefdinir	No dosage adjustment required in the elderly. Safety and efficacy have not been established in children <6 months of age.	A dose of 300 mg once daily is recommended in patients with creatinine clearance <30 mL/minute. The recommended initial dose in patients on chronic hemodialysis is 300 mg or 7 mg/kg every other day.	No dosage adjustment required.	B	Not detected in milk after single 600 mg dose.
Cefditoren	No dosage adjustment required in the elderly. Safety and efficacy have not been established in children <12 years of age.	A dose of 200 mg twice a day is recommended in patients with creatinine clearance 30 to 49 mL/minute and 200 mg once daily in patients with creatinine clearance <30 mL/minute.	No dosage adjustment required in patients with mild to moderate hepatic impairment.	B	Unknown
Cefixime	No dosage adjustment required in the elderly. Safety and efficacy in children <6 months of age have not been established.	Administer 75% of the dose at the standard dosing interval to patients with creatinine clearance 21 to 60 mL/minute. Administer 50% of the dose at the standard dosing interval to patients with creatinine clearance <20 mL/minute or those on continuous ambulatory peritoneal dialysis.	No dosage adjustment required.	B	Unknown
Cefpodoxime	No dosage adjustment required in the elderly. Safety and efficacy in	The dosing interval should be extended to every 24 hours in patients with creatinine clearance <30 mL/minute.	No dosage adjustment required.	B	Yes

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	children <2 months of age have not been established.	In patients maintained on hemodialysis, the dose frequency should be three times/week after hemodialysis.			
Ceftibuten	No dosage adjustment required in the elderly. Safety and efficacy in children <6 months of age have not been established.	A dose of 200 mg every 24 hours or 4.5 mg/kg is recommended in patients with creatinine clearance 30 to 49 mL/minute. A dose of 100 mg every 24 hours or 2.25 mg/kg is recommended in patients with creatinine clearance 5 to 29 mL/minute. Patients undergoing hemodialysis should be given 400 mg or 9 mg/kg at the end of each session.	No dosage adjustment required.	B	Unknown

Adverse Drug Events

Table 7. Adverse Drug Events (%)[4-11]

Adverse Event	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Cardiovascular					
Cardiac failure	a	-	-	-	-
Chest pain	a	-	-	<1	-
Congestive heart failure	-	-	-	<1	-
Hypertension	a	-	-	<1	-
Hypotension	-	-	-	<1	-
Myocardial infarction	a	-	-	-	-
Palpitation	-	-	-	<1	-
Vasodilation	-	-	-	<1	-
Central Nervous System					
Abnormal dreams	-	>0.1<1.0	-	<1	-
Agitation	-	-	-	-	>0.1<1.0
Anxiety	-	-	-	<1	-
Asthenia	0.2	>0.1<1.0	-	<1	-
Cerebral infarction	-	-	-	<1	-
Confusion	a	-	-	<1	-
Dizziness	0.3	>0.1<1.0	<2	<1	1

Adverse Event	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Fatigue	-	-	-	<1	>0.1<1.0
Fever	a	>0.1<1.0	-	<1	>0.1<1.0
Hallucinations	-	-	-	<1	-
Headache	2	2 to 3	<2	1	3
Hyperactivity	0.2	a	-	<1	>0.1<1.0
Hypertonia	-	a	-	-	-
Impaired concentration	-	-	-	<1	-
Insomnia	0.2	>0.1<1.0	-	<1	>0.1<1.0
Involuntary movements	a	-	-	-	-
Irritable behavior	-	-	-	-	>0.1<1.0
Migraine	-	-	-	<1	-
Nervousness	-	>0.1<1.0	-	<1	-
Nightmares	-	-	-	<1	-
Paresthesias	-	-	-	<1	>0.1<1.0
Psychosis	-	-	-	-	a
Rigors	-	-	-	-	>0.1<1.0
Seizures	a	a	<2	a	a
Shakiness	-	-	-	<1	-
Somnolence	0.2	>0.1<1.0	-	<1	>0.1<1.0
Syncope	-	-	-	<1	-
Vertigo	-	-	-	<1	-
Dermatological					
Acne	-	-	-	<1	-
Desquamation	-	-	-	<1	-
Diaper rash	-	-	-	2	>0.1<1.0
Dry skin	-	-	-	<1	-
Erythema multiforme	a	a	<2	a	-
Erythema nodosum	a	-	-	-	-
Exfoliative dermatitis	a	-	-	<1	-
Fungal dermatitis	-	-	-	<1	-
Hair loss	-	-	-	<1	-
Pruritus	0.2	>0.1<1.0	<2	<1	>0.1<1.0
Rash	0.2 to 8.0	>0.1<1.0	<2	1.8	>0.1<1.0
Stevens-Johnson syndrome	a	a	<2	a	a
Sunburn	-	-	-	<1	-
Toxic epidermal necrolysis	a	a	<2	a	a
Urticaria	-	>0.1<1.0	<2	<1	>0.1<1.0
Gastrointestinal					
Abdominal cramps	-	-	-	<1	-
Abdominal pain	0.8 to 1.0	2	3	1.2	1 to 2
Abnormal stools	0.2 to 0.3	-	-	-	-
Aphasia	-	-	-	-	a
Appetite increased	-	>0.1<1.0	-	-	-
Bloody diarrhea	a	-	-	-	-
Colitis	-	a	<2	-	-
Colitis, hemorrhagic	a	-	-	-	-
Constipation	0.3	>0.1<1.0	-	<1	>0.1<1.0
Cutaneous moniliasis	0.9	-	-	-	-
Diarrhea	4 to 17	11 to 15	16	1.2 to 12.8	3 to 4
Dry throat	-	-	-	<1	-
Dyspepsia	0.2 to 0.7	1 to 2	3	<1	2

Adverse Event	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Enterocolitis, acute	a	-	-	-	-
Eructation	-	>0.1<1.0	-	<1	>0.1<1.0
Flatulence	0.7	>0.1<1.0	4	<1	>0.1<1.0
Gastritis	-	-	-	<1	-
Gastrointestinal disorder	-	>0.1<1.0	-	<1	-
Ileus	a	-	-	-	-
Loose stools	-	-	6	-	>0.1to 2.0
Melena	-	-	-	-	a
Nausea/vomiting	0.2 to 3.0	1 to 6	7	1.4 to 3.3	2 to 4
Oral lesions	-	-	-	<1	-
Oral moniliasis	-	>0.1<1.0	-	<1	-
Peptic ulcer	a	-	-	-	-
Pseudomembranous colitis	a	>0.1<1.0	a	<1	a
Rectal disorders	-	-	-	<1	-
Rectorrhagia with hypotension	-	-	-	a	-
Stomatitis	a	>0.1<1.0	-	<1	-
Taste perversion	-	>0.1<1.0	-	<1	>0.1<1.0
Tenesmus	-	-	-	<1	-
Tongue disorder	-	-	-	<1	-
Tooth ache	-	-	-	<1	-
Tooth disorders	-	-	-	<1	-
Ulcerative colitis	-	-	-	a	-
Upper gastrointestinal bleed	a	-	-	-	-
Genitourinary					
Dysmenorrhea	-	-	-	-	-
Dysuria	-	-	-	<1	>0.1<1.0
Genital moniliasis	0.2 to 4.0	3 to 6	<2	1	-
Genital pruritus	-	a	<2	-	-
Hematuria	-	3.0 to 3.1	-	<1	>0.1<1.0
Leukorrhea	0.2	>0.1<1.0	-	-	-
Metrorrhagia	-	-	-	<1	-
Nocturia	-	-	-	<1	-
Penile infection	-	-	-	<1	-
Urine white blood cells increased	-	2.3	-	-	-
Urinary frequency	-	-	-	<1	-
Urinary tract infection	-	-	-	<1	-
Vaginal pain	-	-	-	<1	-
Vaginitis	1	>0.1<1.0	<2	<1	-
Vulvovaginal infections	-	-	-	1.3	-
Hematological					
Agranulocytosis	a	a	-	a	a
Albumin decreased	-	>0.1<1.0	-	<1	-
Anemia	-	-	-	<1	-
Aplastic anemia	a	a	<2	a	a
Basophilia	-	-	-	<1	-
Bleeding tendency	a	-	-	-	-
Coagulation disorder	a	>0.1<1.0	-	-	-
Disseminated intravascular coagulation	a	-	-	a	-
Eosinophilia	0.7 to 1.0	>0.1<1.0	<2	<1	3

Adverse Event	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Granulocytopenia	a	-	-	-	-
Granulocytosis	-	-	-	<1	-
Hematocrit decreased	0.2	2.1 to 2.2	-	<1	-
Hemoglobin decreased	0.3 to 0.5	>0.1<1.0	-	<1	1 to 2
Hemolytic anemia	a	a	<2	a	a
Hemorrhage	a	a	<2	a	a
Idiopathic thrombocytopenia purpura	a	-	-	<1	-
Leukocytosis	-	-	-	<1	-
Leukopenia	0.3	>0.1<1.0	<2	<1	>0.1<1.0
Lymphocytes decreased	0.8 to 1.0	-	-	<1	-
Lymphocytes increased	0.2 to 2.0	>0.1<1.0	-	-	-
Monocytes increased	0.4	-	-	<1	-
Neutropenia	a	>0.1<1.0	<2	<1	a
Pancytopenia	a	a	-	a	a
Platelets increased	0.2 to 1.0	>0.1<1.0	-	-	>0.1≤1.0
Polymorphonuclear neutrophils decreased	0.2 to 1.0	-	-	-	-
Polymorphonuclear neutrophils increased	0.3 to 1.0	-	-	-	-
Positive Coomb's test	-	a	-	<1	-
Prothrombin time increased	-	a	<2	<1	-
Thrombocythemia	-	>0.1<1.0	-	<1	-
Thrombocytopenia	a	-	<2	<1	>0.1<1.0
Thrombocytosis	-	-	-	<1	-
White blood cells decreased	0.7	>0.1<1.0	-	-	-
White blood cells increased	0.3 to 0.9	>0.1<1.0	-	-	-
Hepatic					
Acute liver injury	-	-	-	a	-
Abnormal liver enzymes	0.2 to 1.0	>0.1<1.0	<2	<1	>0.1<1.0
Bilirubin increased	-	a	<2	<1	1
Cholestasis	a	a	<2	a	a
Hepatic dysfunction	a	a	<2	a	-
Hepatitis, transient	a	-	<2	-	-
Jaundice	a	-	<2	-	a
Musculoskeletal					
Back pain	-	-	-	<1	-
Myalgia	-	>0.1<1.0	-	<1	-
Rhabdomyolysis	a	-	-	-	-
Renal					
Acute renal failure	a	-	<2	-	-
Blood urea nitrogen increased	0.3	>0.1<1.0	<2	<1	2 to 4
Creatinine increased	-	a	<2	<1	>0.1<1.0
Microhematuria	1	-	-	-	-
Nephropathy	a	-	-	-	-
Purpuric nephritis	-	-	-	a	-
Renal insufficiency	a	a	<2	a	a
Toxic nephropathy	a	a	<2	a	a
Urine glucose increased	0.9	-	-	-	-
Urine leukocytes increased	0.5 to 2.0	-	-	-	-
Urine protein increased	1 to 2	>0.1<1.0	-	<1	-

Adverse Event	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Urine pH increased	0.2 to 0.8	-	-	-	-
Urine specific gravity increased or decreased	0.1 to 0.6	-	-	-	-
Respiratory					
Acute respiratory failure	a	-	-	-	-
Asthma	-	>0.1<1.0	-	<1	-
Asthmatic shock	a	-	-	-	-
Bronchitis	-	-	-	<1	-
Cough	-	-	-	<1	-
Dyspnea	-	-	-	<1	>0.1<1.0
Epistaxis	-	-	-	<1	-
Nasal congestion	-	-	-	-	>0.1<1.0
Pharyngitis	-	>0.1<1.0	-	-	-
Pleural effusion	-	-	-	<1	-
Pneumonia	-	-	-	<1	-
Pneumonia, drug induced	a	-	-	-	-
Pneumonia, eosinophilic	a	-	-	-	-
Pneumonia, idiopathic interstitial	a	-	-	-	-
Pulmonary infiltrate	-	-	-	a	-
Rhinitis	-	>0.1<1.0	-	<1	-
Sinusitis	-	>0.1<1.0	-	<1	-
Stridor	-	-	-	-	a
Wheezing	-	-	-	<1	-
Miscellaneous					
Abnormal microbiological tests	-	-	-	<1	-
Abscess	-	-	-	<1	-
Allergic vasculitis	a	-	-	-	-
Anaphylaxis	a	a	<2	a	a
Angioedema	a	a	<2	-	-
Anorexia	0.3	>0.1<1.0	-	<1	>0.1<1.0
Bacterial infections	-	-	-	<1	-
Bicarbonate decreased	0.6 to 1.0	-	-	-	-
Calcium decreased	-	>0.1<1.0	-	-	-
Chills	-	-	-	<1	-
Chloride decreased	-	>0.1<1.0	-	-	-
Conjunctivitis	a	-	-	-	-
Dehydration	-	-	-	<1	>0.1<1.0
Dry mouth	0.3	>0.1<1.0	-	<1	>0.1<1.0
Edema	a	-	-	<1	-
Eye irritation	-	-	-	<1	-
Eyelid dermatitis	-	-	-	a	-
Feeling of suffocation	a	-	-	-	-
Fungal infection	-	>0.1<1.0	-	<1	-
Glucose increased	0.9	-	-	-	-
Gout	-	-	-	<1	-
Hematoma	-	-	-	<1	-
Hyperglycemia	-	1.1 to 1.8	-	<1	-
Hyperlipidemia	-	>0.1<1.0	-	-	-
Hyperkalemia	0.2 to 0.3	>0.1<1.0	-	<1	-
Hypoglycemia	-	-	-	<1	-
Hypoproteinemia	-	-	-	<1	-

Adverse Event	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
In-utero exposure with miscarriage	-	-	-	a	-
Loss of consciousness	a	-	-	-	-
Malaise	-	-	-	<1	-
Moniliasis	-	-	-	-	>0.1<1.0
Pain	-	>0.1<1.0	-	<1	-
Parasitic infections	-	-	-	<1	-
Peripheral edema	-	>0.1<1.0	-	<1	-
Phosphorus decreased	0.3 to 0.4	>0.1<1.0	-	-	-
Phosphorus increased	0.6 to 0.9	-	-	-	-
Serum sickness-like reaction	a	a	<2	a	a
Shock	a	-	-	-	-
Sodium decreased	-	>0.1<1.0	-	<1	-
Superinfection	a	a	<2	-	-
Sweating	-	>0.1<1.0	-	<1	-
Thirst	-	>0.1<1.0	-	<1	-
Tinnitus	-	-	-	<1	-
Weight increased	-	-	-	<1	-

a Percent not specified.
- Event not reported.

Contraindications

Table 8. Contraindications[4-11]

Contraindications	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Known allergy to cephalosporins	a	-	-	-	-
Do not administer to patients with milk protein hypersensitivity (not lactose intolerance)	a	a	a	a	-

Warnings/Precautions

Table 9. Warnings and Precautions[4-11]

Warnings and Precautions	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Hypersensitivity reactions; determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs	a	a	a	a	a
Pseudomembranous colitis been reported with nearly all antibacterial agents	-	a	a	a	a
Renal function impairment; lower doses should be used in this patient population	-	-	-	a	a
Superinfection; prolonged treatment with broad-spectrum antibiotics may result in the emergence and overgrowth of resistant organisms	-	a	a	a	a

Warnings and Precautions	Cefdinir	Cefditoren	Cefixime	Cefpodoxime	Ceftibuten
Resistance; antibiotic use in the absence of a bacterial infection or for prophylaxis is unlikely to provide benefit to the patient and increases the risk of developing drug-resistant bacteria	-	a	a	-	-
Not recommended when prolonged antibiotic treatment is necessary, as other pivalate-containing compounds have caused carnitine deficiency when used over several months	-	a	-	-	-
Coagulation abnormalities; cephalosporins may be associated with a fall in prothrombin activity	-	a	a	-	-
Seizures; cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced	-	-	a	-	a
Special risk patients; use with caution in individuals with histories of gastrointestinal disease, particularly colitis	-	-	a	-	-

Drug Interactions

No clinically significant drug interactions were noted in the clinical literature.[58]

Dosage and Administration

Table 10. Dosing and Administration[4-11]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Cefdinir	Acute exacerbations of chronic bronchitis, sinusitis and pharyngitis/tonsillitis: 300 mg every 12 hours or 600 mg QD Community-acquired pneumonia, skin and skin structure infections: 300 mg every 12 hours	Acute otitis media, sinusitis and pharyngitis/tonsillitis in patients six months to 12 years of age: 7 mg/kg every 12 hours or 14 mg/kg QD* Skin and skin structure infections: 7 mg/kg every 12 hours* Safety and efficacy have not been established in children <6 months of age.	Capsule: 300 mg Powder for oral suspension: 125 mg/5 mL 250 mg/5 mL
Cefditoren	Acute bacterial exacerbations of chronic bronchitis and community-acquired pneumonia: 400 mg BID	Safety and efficacy have not been established in children <12 years of age.	Tablet: 200 mg 400 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Pharyngitis/tonsillitis and skin and skin structure infections: 200 mg BID		
Cefixime	Cervical/urethral gonococcal infections: 400 mg as a single dose Urinary tract infections, acute bacterial exacerbations of chronic bronchitis, pharyngitis and/or tonsillitis, acute bronchitis and otitis media†: 200 mg every 12 hours or 400 mg QD	Urinary tract infections, acute bacterial exacerbations of chronic bronchitis, pharyngitis and/or tonsillitis, acute bronchitis and otitis media in children six months to 12 years of age†: 4 mg/kg every 12 hours or 8 mg/kg QD‡	Powder for oral suspension: 100 mg/5 mL 200 mg/5 mL Tablet: 400 mg
Cefpodoxime	Acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia and sinusitis: 200 mg every 12 hours Gonorrhea and rectal gonococcal infections: 200 mg as a single dose Pharyngitis/tonsillitis and urinary tract infections: 100 mg every 12 hours Skin and skin structure infections: 400 mg every 12 hours	Otitis media and sinusitis in children two months to 12 years of age: 5 mg/kg every 12 hours; maximum 200 mg/dose and 400 mg/day Pharyngitis/tonsillitis: 5 mg/kg every 12 hours; maximum 100 mg/dose and 200 mg/day Safety and efficacy in children <2 months of age have not been established.	Powder for oral suspension: 50 mg/5 mL 100 mg/5 mL Tablet: 100 mg 200 mg
Ceftibuten	Acute bacterial exacerbations of chronic bronchitis, otitis media and pharyngitis and/or tonsillitis: 400 mg QD	Acute bacterial exacerbations of chronic bronchitis, otitis media and pharyngitis and/or tonsillitis§: 9 mg/kg QD; maximum 400 mg QD Safety and efficacy in children <6 months of age have not been established.	Capsule: 400 mg Powder for oral suspension: 90 mg/5 mL 180 mg/5 mL

*Patients weighing ≥43 kg should receive the maximum daily dose of 600 mg.
†Otitis media should be treated with cefixime suspension, not cefixime tablets. The suspension results in higher peak blood levels compared to the tablet when administered at the same dose.
‡Children weighting >50 kg should receive the recommended adult dose of cefixime.
§Patients weighing ≥45 kg should receive the maximum daily dose of 400 mg.
BID=twice daily, QD=once daily

Clinical Guidelines

The clinical guidelines contained in Table 11 are summarized globally and are not limited to the role of the third generation cephalosporins. However, the summary of the Chronic Obstructive Pulmonary Disease (COPD) guidelines focuses only on the treatment of exacerbations which have a bacterial component. The global treatment strategy for COPD is not discussed in this summary.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
Infectious Diseases Society of America/ American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[59]	General recommendations · Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns. · Once the etiology of community-acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. Empiric therapy - outpatient treatment · For previously healthy patients with no risk factors for drug resistant *Streptococcus pneumoniae* infection, a macrolide (azithromycin, clarithromycin, or erythromycin) can be used. Doxycycline may also be an alternate option. · A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant *S pneumoniae*, or for patients with comorbidities, such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs. Fluoroquinolones may also be used for patients who have used antimicrobials within the previous three months. Other preferred options for these patients would be the combination of a β-lactam (ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate. Empiric therapy - inpatient, non-intensive care unit treatment · A respiratory fluoroquinolone or a combination of a β-lactam plus a macrolide is recommended. · Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem may also be used for selected patients. · A respiratory fluoroquinolone should be used for penicillin allergic patients. Empiric therapy - inpatient, intensive care unit treatment · A β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. · For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended. · For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin. · The antipneumococcal, antipseudomonal β-lactams listed above can also be used with either an aminoglycoside and azithromycin, or an aminoglycoside and an antipneumococcal fluoroquinolone. · For penicillin-allergic patients, substitute aztreonam for the above β-lactam for *Pseudomonas* infection. Pathogen-directed therapy · *S pneumonia* (penicillin non-resistant)- penicillin G or amoxicillin preferred; alternative agents include macrolides, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren or parenteral

Clinical Guideline	Recommendations
	cefuroxime, ceftriaxone or cefotaxime), clindamycin, doxycycline or a respiratory fluoroquinolone. · *S pneumonia* (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day). · *Haemophilus influenza* (non-β-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. · *H influenza* (β-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. · *Mycoplasma pneumonia/Chlamydia pneumonia*- macrolide, tetracycline preferred; alternative agent is fluoroquinolone. · *Legionella* species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline. · *Chlamydia psittaci*- tetracycline preferred; alternative agent is a macrolide. · *Coxiella burnetii*- tetracycline preferred; alternative agent is a macrolide. · *Francisella tularensis*- doxycycline preferred; alternative agents include gentamicin or streptomycin. · *Yersinia pestis*- streptomycin, gentamicin recommend; alternative agents include doxycycline or fluoroquinolone. · *Bacillus anthracis* (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol, or a β-lactam if susceptible. · *Enterobacteriaceae*- third generation cephalosporin, carbapenem; alternative agents include a β-lactam/β-lactamase inhibitor or a fluoroquinolone. · *Pseudomonas aeruginosa*- antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin. · *Burkholderia pseudomallei*- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP). · *Acinetobacter* species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin. · *Staphylococcus aureus* (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin. · *S aureus* (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP. · *Bordetella pertussis*- macrolide preferred; alternative agent is SMX/TMP. · Anaerobe (aspiration)- β-lactam/β-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem. · Influenza virus- oseltamivir or zanamivir preferred. · *Mycobacterium tuberculosis*- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred. · *Coccidioides* species- no therapy generally recommended in normal host for uncomplicated infection; if therapy desired, itraconazole or fluconazole preferred; alternative agent is amphotericin B. · *Histoplasmosis*- itraconazole preferred; alternative agent is amphotericin B.

Clinical Guideline	Recommendations
	· *Blastomycosis*- itraconazole preferred; alternative agent is amphotericin B. · Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting *S pneumonia* and *S aureus.*
American College of Chest Physicians: **Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement (2005)**[60]	· The oral route for medications is recommended if the patient can tolerate it, and if the availability and activity of the agents are adequate. · Severity of illness, patient age, comorbidities, concomitant medications, and ease of administration are all factors that can impact the empiric treatment decision. · The use of a macrolide, doxycycline, or fluoroquinolone antibacterial agent is recommended by both the Infectious Disease Society of America and the American Thoracic Society consensus guidelines as appropriate empiric outpatient treatment for low-risk patients. · Amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime, or cefprozil) are alternatives for low-risk patients. · A patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with a β-lactam/macrolide combination or an antipneumococcal fluoroquinolone. · Double therapy with either a β-lactam/macrolide combination or a β-lactam/antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for intensive care unit admission but have chosen to remain in the home.
Infectious Diseases Society of America/ American Thoracic Society: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2004)**[61]	· Empiric therapy for hospital-acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia should include agents from a different class than the patient has recently received. · Judicious use of combination therapy in hospital-acquired pneumonia for a specific pathogen is recommended with consideration of short-duration (five days) aminoglycoside therapy when used in combination with β-lactam to treat *P aeruginosa* pneumonia. · De-escalation of antibiotics should be considered once results are available of lower respiratory tract cultures and patient's clinical response. · For patients with uncomplicated hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia who have received initially appropriate therapy and have had a good clinical response with no evidence of infection with nonfermenting gram-negative bacilli, a shorter duration of antibiotic therapy (seven to eight days) is recommended. · The following initial empiric therapy is recommended for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with early onset of disease, no known risk factors for multidrug-resistant pathogens and any disease severity: ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam or ertapenem. · The following initial empiric therapy is recommended for hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia in patients with late onset of disease or known risk factors for multidrug-resistant pathogens and all disease severity: antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/ β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal

Clinical Guideline	Recommendations
	fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin.
American Academy of Pediatrics and American Academy of Family Physicians, Subcommittee on Management of Acute Otitis Media: **Diagnosis and Management of Acute Otitis Media (2004)**[62]	· Treatment of existing pain, generally with acetaminophen or ibuprofen, is recommended regardless of initiation of antibacterial treatment. · Amoxicillin (80 to 90 mg/kg/day) is considered first-line therapy for the treatment of acute otitis media in most children, when the decision is made to treat with an antibacterial agent. This is in part due to amoxicillin's effectiveness when used in sufficient doses against susceptible organisms; other factors include its safety, acceptable taste, and narrow microbiologic spectrum. · Approximately 80% of patients with acute otitis media will respond to treatment with high-dose amoxicillin. · Patients with a fever ≥102°F or moderate-to-severe pain (severe illness) and/or who require additional coverage for *H influenzae* and *Moraxella catarrhalis* should be treated with high dose amoxicillin/clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate in two divided doses). · Those patients who have failed first-line treatment should be initiated on amoxicillin/clavulanate (90 mg/kg/day of amoxicillin component divided in two doses). · Patients who have failed to improve while receiving amoxicillin should not be treated with SMX/TMP or erythromycin/sulfisoxazole. · Patients who fail treatment with amoxicillin/clavulanate should be treated with parenteral ceftriaxone. · For patients with fever and severe symptoms (including severe vomiting) that precludes the administration of oral antibacterial agents, a three-day course of ceftriaxone, administered intravenously or intramuscularly, should be initiated at the onset of symptoms. Ceftriaxone should also be initiated via intravenous route for three days in a patient who fails amoxicillin/clavulanate. <u>Special populations</u> · In patients with a history of non-type-I penicillin allergy, cefdinir, cefpodoxime or cefuroxime are considered alternatives to amoxicillin. · In patients with a history of type-1 penicillin allergy, azithromycin or clarithromycin can be used. Other options include erythromycin/sulfisoxazole, SMX/TMP or clindamycin. · Parenteral therapy with ceftriaxone may be used in patients who cannot tolerate oral therapy.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis (2002)**[63]	· Penicillin is the drug of choice for the treatment of group A streptococcal pharyngitis. · Amoxicillin may be used in place of penicillin based mainly on taste. · Erythromycin is an alternative in patients with a penicillin allergy. · First generation cephalosporins are acceptable alternatives in patients with a non-type 1 penicillin allergy. · Clindamycin may be used in patients who are unable to tolerate β-lactam antibiotics and who are infected with erythromycin-resistant group A *Streptococcus*. · For patients with multiple, recurrent episodes of pharyngitis, a 10-day course of clindamycin or amoxicillin/clavulanic acid is recommended. Alternatively, one dose of intramuscular benzathine penicillin G or benzathine penicillin G plus a four-day course of rifampin can be used.

Clinical Guideline	Recommendations
American Heart Association: **Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis (2009)**[64]	Primary prevention (treatment of Streptococcal tonsillopharyngitis) · The oral antibiotics of choice are penicillin V and amoxicillin. · Penicillin V, amoxicillin or benzathine penicillin G is recommended. · In patients allergic to penicillin, a narrow spectrum cephalosporin, clindamycin, azithromycin or clarithromycin may be used. · In symptomatic patients who fail an initial course of penicillin, retreatment with a narrow spectrum cephalosporin, clindamycin, amoxicillin/clavulanate or a combination of penicillin plus rifampin is recommended. · In clinical trials, a once-daily amoxicillin (Moxatag®) was shown to be effective for group A streptococcal pharyngitis. It has the advantage of being dosed once-daily which may enhance adherence. Secondary prevention (prevention of recurrent attacks of rheumatic fever) · Benzathine penicillin G, penicillin V or sufadiazine are recommended. · In patients allergic to penicillin, a macrolide or azalide are recommended.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2011)**[65]	Pharyngitis · Penicillin is the drug of choice. Amoxicillin is an acceptable alternative due to poor palatability of penicillin suspension. · Penicillin-allergic patients should be treated with cephalosporins, erythromycin or clindamycin. · Alternative medications include macrolides, cephalexin, clindamycin, amoxicillin/clavulanate, and rocephin. · Prevention of recurrent rheumatic fever requires continuous antimicrobial prophylaxis. Bacterial sinusitis · Antibiotics should be reserved for patients who fail decongestant therapy, those presenting with symptoms and signs of more severe disease, and those with complications of acute sinusitis. · Amoxicillin is the first-line drug of choice. · SMX/TMP is a potential first-line antibiotic, though clinicians may avoid its use due to concerns regarding resistant *S pneumoniae*. It should generally be reserved for patients who are allergic to amoxicillin. · For patients allergic to both penicillin and SMX/TMP, macrolides may be prescribed. Cephalosporins may be considered, but there is about a 10% cross-reaction between cephalosporins and amoxicillin. · In general, fluoroquinolones should not be used since they are generally inactive against pneumococci. · Amoxicillin/clavulanate or a macrolide may be used in a patient who fails an initial round of treatment. A fluoroquinolone with pneumococcal coverage may be considered, except in patients who are skeletally immature. · Additional second-line agents for patients infected with penicillin and SMX/TMP resistant bacteria include cefuroxime, cefpodoxime, cefprozil, cefdinir, cefaclor, clarithromycin, azithromycin, levofloxacin or moxifloxacin (except in patients who are skeletally immature).
American Academy of Pediatrics: **Management of Sinusitis (2001)**[66]	· Amoxicillin is considered first-line therapy for acute bacterial sinusitis due to its general effectiveness, safety, tolerability, and narrow spectrum. · For children younger than two years of age with uncomplicated bacterial

Clinical Guideline	Recommendations
	sinusitis that is mild to moderate in severity who do not attend day care and have not recently been treated with an antibiotic, amoxicillin is recommended at 45 mg/kg/day in two divided doses or 90 mg/kg/day in two divided doses. · If the patient has an allergic reaction to amoxicillin that is not a type 1 hypersensitivity reaction, then cefdinir, cefuroxime, or cefpodoxime can be used. In cases of serious allergic reaction to amoxicillin, then clarithromycin, azithromycin, or clindamycin can be used. · If the patient has an inadequate response, has recently been treated with an antibiotic, has a moderate or severe illness, or attends daycare, high dose amoxicillin/clavulanate (80 to 90 mg/kg/day in two divided doses) should be used instead. Alternatives include cefdinir, cefuroxime, or cefpodoxime.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[67]	Antimicrobial therapy based on the presumptive pathogen identified by positive Gram stain · *S pneumonia* - vancomycin plus third-generation cephalosporin; alternative agents are meropenem or a fluoroquinolone. · *Neisseria meningitides* - third generation cephalosporin; alternative agents include penicillin G, ampicillin, chloramphenicol, fluoroquinolones, or aztreonam. · *Listeria monocytogenes* and *Streptococcus agalactiae* - ampicillin or penicillin G; alternative agents include SMX/TMP or meropenem (for *L monocytogenes*) and a third generation cephalosporin (for *S agalactiae*). · *H influenza* - third generation cephalosporin; alterative agents include chloramphenicol, cefepime, meropenem, or a fluoroquinolone. · *Escherichia coli* - third generation cephalosporin; alternative agents include cefepime, meropenem, aztreonam, fluoroquinolone, or SMX/TMP. Empiric therapy based on age and predisposing condition · Age <one month, *S agalactiae, E coli, L monocytogenes, Klebsiella* species: ampicillin plus cefotaxime or ampicillin plus aminoglycoside. · Age one to 23 months, *S pneumoniae, N meningitides, S agalactiae, H influenza, E coli*: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). · Age two to 50 years, *N meningitides, S pneumoniae*: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). · Age >50 years, *S pneumoniae, N meningitides, L monocytogenes, aerobic gram-negative bacilli*: vancomycin plus ampicillin plus third generation cephalosporin (ceftriaxone or cefotaxime). · Basilar skull fracture, *S pneumoniae, H influenza*, group A β-hemolytic streptococci: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). · Penetrating head trauma, *S aureus*, coagulase-negative staphylococci, aerobic gram-negative bacilli: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. · Post-neurosurgery, aerobic gram-negative bacilli, *S aureus*, coagulase-negative staphylococci: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. · Cerebrospinal fluid shunt, coagulase-negative staphylococci, *S aureus*, aerobic gram-negative bacilli, *Propionibacterium acnes*: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus

Clinical Guideline	Recommendations
	meropenem. Specific antimicrobial therapy based on pathogen and susceptibility · *S pneumonia:* o Penicillin minimum inhibitory concentration (MIC) <0.1 µg/mL: penicillin G or ampicillin, alternative therapies include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. o Penicillin MIC 0.1 to 1.0 µg/mL: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include cefepime, meropenem. o Penicillin MIC ≥2 µg/mL: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2µg/mL), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). o Cefotaxime or ceftriaxone MIC ≥1 µg/mL: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2 µg/mL), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). · *N meningitides:* o Penicillin MIC <0.1 µg/mL: penicillin G or ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. o Penicillin MIC 0.1 to 1.0 µ/mL: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include chloramphenicol, fluoroquinolone, meropenem. · *L monocytogenes*: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include SMX/TMP, meropenem. · *S agalactiae*: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime). · *E coli* or *Enterobacteriaceae:* third generation cephalosporin, alternative agents include aztreonam, fluoroquinolone, meropenem, SMX/TMP, ampicillin. · *P aeruginosa:* cefepime or ceftazidime (addition of aminoglycoside should be considered), alternative agents include aztreonam, ciprofloxacin, meropenem (addition of aminoglycoside should be considered). · *H influenza:* o β-lactamase negative: ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), cefepime, chloramphenicol, fluoroquinolone. o β-lactamase positive: third generation cephalosporin, alternative agents include cefepime, chloramphenicol, fluoroquinolone. · *S aureus* o Methicillin susceptible: nafcillin or oxacillin, alternative agents include vancomycin, meropenem. o Methicillin resistant: vancomycin (consider addition of rifampin), alternative agents include SMX/TMP, linezolid. · *Staphylococcus epidermidis*: vancomycin (consider addition of rifampin), alternative agent is linezolid.

Clinical Guideline	Recommendations
	· *Enterococcus* species: o Ampicillin susceptible: ampicillin plus gentamicin. o Ampicillin resistant: vancomycin plus gentamicin. o Ampicillin and vancomycin resistant: linezolid.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)**[68]	General observations · Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first or second generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S *aureus* (MRSA) strains. · In patients with severe infection or infection that has progressed while on empirical antibiotic treatment, selection of therapeutic agents should be based on results of the gram stain, culture and drug susceptibility analysis. · In the case of *S aureus*, the clinician should assume the organism is resistant due to the high prevalence of community-associated MRSA strains. Agents effective against MRSA should be used in patients who have severe infections requiring hospitalization or those who have not responded to attempts to eradicate the infection (vancomycin, linezolid, daptomycin). Step-down treatment to other agents may be possible based on susceptibility tests. · An increase in the macrolide resistance of *Streptococcus pyogenes* has been noted, while 99.5% of strains remain susceptible to clindamycin and 100% to penicillin. · Osteomyelitis typically requires treatment for four to six weeks. Animal bites · The decision to administer oral or intravenous antibiotic therapy is determined by the depth and severity of the wound and the time elapsed since the bite. · Appropriate first-line therapy includes oral amoxicillin/clavulanate, doxycycline, or penicillin VK plus dicloxacillin. Other options include fluoroquinolones, SMX/TMP, and cefuroxime. The patient may also require an additional agent that is active against anaerobes, such as metronidazole or clindamycin. · Intravenous options include ampicillin/sulbactam, piperacillin/tazobactam, second generation cephalosporins, and carbapenems. Second- and third-generation cephalosporins may be used but require the addition of an antianaerobic agent. Animal contact · Though no randomized controlled trials exist for treatment of cutaneous anthrax, most data indicate that penicillin is effective. Less evidence supports the use of tetracyclines, chloramphenicol and erythromycin. · Bioterrorism-related anthrax should be treated with a fluoroquinolone until susceptibility tests are available, as inhalation may also have occurred. · Cat scratch disease and bacillary angiomatosis may be treated with azithromycin, erythromycin or doxycycline. Other alternatives include rifampin, SMX/TMP and ciprofloxacin. · Erysipeloid cutaneous infections should be treated with penicillin or amoxicillin; cephalosporins, clindamycin and fluoroquinolones are

Clinical Guideline	Recommendations
	effective alternatives. · Glanders may be treated with ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin. · Streptomycin has been the drug of choice for bubonic plague. Tetracycline and chloramphenicol are also appropriate. Fluoroquinolones are alternative agents. · Ciprofloxacin has been suggested for both treatment and prevention of plague (bubonic and pneumonic) due to biowarfare agents. · Streptomycin is considered the drug of choice for tularemia. Acutely ill patients should receive streptomycin or gentamicin. Mild to moderate disease may be treated with oral tetracycline or doxycycline. <u>Cellulitis</u> · Cellulitis is commonly treatable with oral antibiotics, such as dicloxacillin, cephalexin, clindamycin or erythromycin. · For severe infection, the treatment of choice is either a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin. · In patients with severe penicillin allergy, clindamycin or vancomycin is indicated. · To reduce the risk of recurrence, it is important to keep the affected area well-hydrated and to reduce edema with elevation or compression stockings. Prophylactic treatment with monthly intramuscular benzathine penicillin, oral erythromycin, or penicillin V is also an option. <u>Erysipelas</u> · Oral or intravenous penicillin is the first-line treatment depending on severity. · In the presence or suspicion of staphylococcal infection, a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin is indicated. <u>Human bites</u> · Clenched-fist injuries typically require hospitalization and intravenous ampicillin/sulbactam, cefoxitin or one of the carbapenems. · Fluoroquinolones plus clindamycin or SMX/TMP plus metronidazole can be used in patients with severe penicillin allergy. <u>Impetigo</u> · Penicillinase-resistant penicillins or first generation cephalosporins are the preferred agents. · Erythromycin is indicated in the presence of pyoderma, but use is limited by erythromycin-resistant strains of *S aureus* and *S pyogenes.* · Topical therapy with mupirocin is equivalent to oral systemic antibiotics. <u>Necrotizing infections</u> · Antimicrobial therapy (coverage against aerobes and anaerobes) should be directed at the specific pathogen and appropriate doses should be used until operative procedures are no longer needed. · The combination of ampicillin/sulbactam, clindamycin and ciprofloxacin is first-line therapy for community-acquired mixed infection. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy,

Clinical Guideline	Recommendations
	alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. · Clindamycin and penicillin should be used in necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A streptococci. The efficacy of intravenous gamma globulin in these cases is still under investigation. · *Streptococcus* infection should be treated with high-dose penicillin or ampicillin plus clindamycin. · *S aureus* infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin/dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. · In gas gangrene, the efficacy of hyperbaric oxygen is inconclusive. Standard antibiotic treatment is penicillin plus clindamycin. <u>Soft-tissue infections caused by community-acquired MRSA</u> · They are often susceptible to non-β-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, SMX/TMP, rifampin, or fluoroquinolones, specifically levofloxacin, gatifloxacin or moxifloxacin. <u>Surgical site infections</u> · Surgical site infections often resolve without the use of antibiotics. · In patients with a temperature >38.5°C, pulse rate >100 beats/minute or erythema diameter >5 cm from incision with induration or necrosis, a short course of antibiotics is recommended. · For wounds of the perineum or operation on the gastrointestinal tract or female genital tract, cefotetan or ampicillin/sulbactam or a fluoroquinolone plus clindamycin is recommended. · For clean wounds on the trunk, head, neck or extremities, cefazolin, oxacillin or clindamycin are recommended. <u>Immunocompromised patients</u> · In neutropenic patients, empiric broad-spectrum antibacterial therapy is recommended at the first sign of infection including fever. · For gram-negative infections, monotherapy with carbapenems, cephalosporins with antipseudomonal activity, and piperacillin/tazobactam, are all appropriate. Recommended combination therapy regimens are (1) an aminoglycoside plus either an antipseudomonal penicillin or an extended-spectrum cephalosporin, or (2) an extended-spectrum penicillin plus ciprofloxacin. Adjunct treatment with granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor is recommended. · For gram-positive infections, vancomycin is not recommended for empirical antibiotic therapy because of resistance; linezolid or daptomycin are appropriate alternatives to vancomycin. · For *Nocardia* infection, first-line therapy is SMX/TMP. Other sulfonamide antibiotics and imipenem are also appropriate. · Empirical antifungal therapy is a common practice in neutropenic patients with persistent fever. Amphotericin B, caspofungin and voriconazole are appropriate. · Amphotericin B and its lipid formulations have been the gold standard to

Clinical Guideline	Recommendations
	treatment for yeast and fungal infections in neutropenic patients. Caspofungin and voriconazole appear to be as effective as amphotericin B and with less serious acute toxicity but are more expensive. · Treatment of non-tubercular mycobacterial infections of the skin and soft tissues requires combination therapy that should include a macrolide. · Cutaneous *Nocardia* infections should be treated with SMX/TMP, the treatment of choice. Other sulfa antibiotics and imipenem are also effective. · Initial therapy for Cryptococcal cellulitis is fluconazole, which is also used to complete therapy after patients have shown an initial response to amphotericin B and 5-flucytosine induction therapy. · Amphotericin B is recommended in patients with cellular immune deficiency and disseminated histoplasmosis. Itraconazole may replace amphotericin B after one to two weeks to complete at least six to 12 months of treatment. · Prevention of viral reactivation with oral acyclovir, famciclovir or valacyclovir is an important component of the treatment of cutaneous varicella zoster virus. · Acyclovir is the treatment of choice for herpes simplex virus infections, though famciclovir and valacyclovir are also highly effective. · Prolonged ganciclovir therapy is the treatment of choice for cutaneous cytomegalovirus.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic Foot Infections (2012)**[69]	· Clinically uninfected wounds should not be treated with antibiotic therapy. · Antibiotic therapy is recommended for all infected wounds but this is often insufficient unless combined with appropriate wound care. · Clinicians should select an empiric antibiotic regimen based on the severity of the infection and the likely etiologic agent. o For mild to moderate infections in patients who have not recently received antibiotic treatment, therapy should target aerobic gram-positive cocci. o For most severe infections, broad-spectrum empiric antibiotic therapy should be started, pending culture results and antibiotic susceptibility data. o Empiric therapy directed at *Pseudomonas aeruginosa* is usually unnecessary except for patients with risk factors for true infection with this organism. o Consider providing empiric therapy directed against *methicillin-resistant Staphylococcus aureus* (MRSA) in a patient with a prior history of MRSA infection or colonization or when the local prevalence of MRSA colonization or infection is high or if the infection is clinically severe. · Targeted therapy should be based on the results of culture and sensitivity testing of a wound specimen as well as the patient's clinical response to the empiric regimen. · The route of therapy should be based on infection severity. Parenteral therapy is recommended for all severe, and some moderate, diabetic foot infections, at least initially, switching to oral agents when the patient is systemically well and culture results are available. Clinicians can use oral antibiotics with high bioavailability alone in most mild, and in many moderate, infections and topical therapy for selected mild superficial infections.

Clinical Guideline	Recommendations
	· Antibiotic therapy should continue until, but not after the resolution infection, but not through complete healing of the wound. An initial antibiotic course for a soft tissue infection of about one to two weeks for mild infections and two to three weeks for moderate to severe infections. · Based on the results of the available studies, no single drug or combination of agents appears to be superior to any others. · For infections of mild severity, the recommended antibiotic agents include: dicloxacillin, clindamycin, cephalexin, levofloxacin and amoxicillin-clavulanate. Doxycycline or trimethoprim/sulfamethoxazole may be used for MRSA. · For moderate or severe infections, the recommended antibiotic agents include: levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, ertapenem, tigecycline, levofloxacin or ciprofloxacin with clindamycin, Imipenem-cilastatin. If MRSA is suspected, linezolid, daptomycin or vancomycin may be used. Piperacillin-tazobactam may be an option if *Pseudomonas aeruginosa* is a concern.
American College of Obstetricians and Gynecologists: **Practice Bulletin: Treatment of Urinary Tract Infections in Nonpregnant Women (2008)**[70]	· Most urinary tract infections are caused by *E coli* (80 to 90%). · Other causes of urinary tract infections include *Staphylococcus saprophyticus*, *Proteus*, *Pseudomonas*, *Klebsiella* and *Enterobacter* species. · Treatment options include SMX/TMP (preferred), trimethoprim, ciprofloxacin, levofloxacin, norfloxacin, gatifloxacin (all three-day regimens), nitrofurantoin macrocrystals, nitrofurantoin monohydrate/macrocrystals (seven-day regimens) and fosfomycin tromethamine (single dose). · First generation cephalosporins and amoxicillin are less effective than the above agents due to resistance and rapid excretion from the urinary tract. · B-lactams are not first-line therapy in acute cystitis unless the causative organism is gram-positive, in which case amoxicillin or amoxicillin/clavulanate may be used. · Women with frequent recurrences may be treated with once daily nitrofurantoin, norfloxacin, ciprofloxacin, trimethoprim, SMX/TMP or any other agent listed above for six to 12 months and then be reassessed. · SMX/TMP is considered the preferred treatment for uncomplicated cystitis except in areas where resistance is common. · Fluoroquinolones should not be used first-line in areas where SMX/TMP resistance is uncommon. · Acute pyelonephritis in acutely ill patients should be treated with parenteral broad-spectrum antibiotics. If gram-positive organisms are suspected, amoxicillin, ampicillin or a cephalosporin may be used. In other cases β-lactams are no longer recommended. · First-line treatment for pyelonephritis is now a fluoroquinolone. SMX/TMP may be used in areas of low resistance. · Parenteral treatment options include an aminoglycoside with ampicillin or piperacillin, a first generation cephalosporin, aztreonam, piperacillin/tazobactam, or a parenteral fluoroquinolone alone or in combination.
Infectious Diseases Society of America:	Acute uncomplicated bacterial cystitis · Taking into consideration availability, allergy history and tolerance the

Clinical Guideline	Recommendations
International Clinical Practice Guidelines for the Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women: A 2010 Update by the Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease (2011)[71]	following antimicrobials are recommended: nitrofurantoin monohydrate/macrocrystals, SMX/TMP, fosfomycin, pivmecillinam*. · Fluoroquinolones (ofloxacin, ciprofloxacin and levofloxacin) are recommended as alternative agents if the above agents cannot be used. Although highly efficacious, fluoroquinolones (ofloxacin, ciprofloxacin and levofloxacin) should be reserved for important uses other than acute cystitis due to increasing resistance. · β-lactams (amoxicillin/clavulanate, cefdinir, and cefpodoxime) are also recommended as alternative agents. Due to poor efficacy and antimicrobial resistance, amoxicillin and ampicillin should not be used as monotherapy. <u>Acute pyelonephritis</u> · In patients not requiring hospitalization and where the prevalence of resistance in the community is not known to exceed 10%, oral ciprofloxacin with or without an initial intravenous loading dose is appropriate. · An initial one-time intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended if prevalence of fluoroquinolone resistance exceeds 10%. · In patients not requiring hospitalization and where the prevalence of resistance in the community is not known to exceed 10%, a once-daily fluoroquinolone (e.g., ciprofloxacin, levofloxacin) is appropriate. · If the pathogen is known to be susceptible, oral SMX/TMP is recommended. When the susceptibility is not known, an initial intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended. · Oral β-lactam agents are less effective than other available agents. Therefore if an oral β-lactam agent is used, an initial intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended. · For women with pyelonephritis requiring hospitalization, an intravenous antimicrobial regimen, such as a fluoroquinolone; an aminoglycoside, with or without ampicillin; an extended-spectrum cephalosporin or extended-spectrum penicillin, with or without an aminoglycoside; or a carbapenem should be initial treatment.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2010)[72]**	<u>Chancroid</u> · Azithromcyin, ceftriaxone, ciprofloxacin (contraindicated in pregnant or lactating women) or erythromycin are recommended treatment strategies. <u>Genital herpes simplex virus</u> · First episodes should be treated with acyclovir, famciclovir, or valcyclovir. · Acyclovir, famciclovir or valcyclovir may be used as suppressive therapy, though famciclovir may be somewhat less effective for suppression of viral shedding. Ease of administration and cost are important considerations for prolonged treatment. · Episodic treatment requires initiation of therapy within one day of lesion onset or during the prodrome that precedes outbreak.

Clinical Guideline	Recommendations
	· Intravenous acyclovir is recommended for severe disease. Granuloma inguinale · Doxycycline is recommended. · Alternative agents include azithromycin, ciprofloxacin, erythromycin or SMX/TMP. · The addition of an aminoglycoside may be considered if improvement is not evident within the first few days of therapy. Lymphogranuloma venereum · Doxycycline is recommended. · An alternative agent is erythromycin. · Clinical data are lacking, though azithromycin is probably effective. · Fluoroquinolone treatment may also be effective, though extended treatment intervals are likely required. · Pregnant and lactating women should be treated with erythromycin. Azithromycin may be an alternative but clinical data are lacking. Syphilis · Penicillin G is the preferred drug for all stages of syphilis. Alternative agents include doxycycline and tetracycline. Limited studies suggest that ceftriaxone is effective. · Azithromycin may be effective in early syphilis but should only be used when treatment with penicillin G or doxycycline is not feasible. It should not be used in pregnant women and men who have sex with men. · Penicillin G is the only therapy recommended during pregnancy. Pregnant women with an allergy to penicillin should be desensitized. · Benzathine penicillin G is recommended for primary and secondary syphilis. · Infants ≥1 month of age with primary or secondary syphilis should be treated with benzathine penicillin G. · Early latent syphilis should be treated with benzathine penicillin G in patients with normal cerebrospinal fluid examinations. · Late latent syphilis or latent syphilis of unknown duration should be treated with benzathine penicillin G in patients with normal cerebrospinal fluid examinations. Alternative agents include doxycycline or tetracycline. · Patients with tertiary syphilis with no evidence of neurosyphilis should be treated with benzathine penicillin G. · Patients with neurosyphilis should be treated with aqueous crystalline penicillin G. An alternative regimen in patients in whom compliance can be assured is procaine penicillin plus probenecid. · Congenital syphilis: o Proven or highly probably disease with abnormal physical exam, serum quantitative serologic titer fourfold higher than the mother's titer or positive darkfield test of body fluids should be treated with aqueous crystalline penicillin G or procaine penicillin G. o Normal physical exam and serum quantitative tier same or less than fourfold the maternal tier and the mother was not treated, inadequately treated or has no documentation of treatment or the mother was treated with erythromycin or other non-penicillin

Clinical Guideline	Recommendations
	regimen or the mother received <4 weeks of treatment before delivery should be treated with aqueous crystalline penicillin G, procaine penicillin G, or benzathine penicillin G. o Normal physical exam with serum quantitative titer the same or less than fourfold the maternal titer and the mother was treated during pregnancy, treatment was appropriate and administered for >4 weeks before delivery and the mother has no evidence of reinfection or relapse should be treated with benzathine penicillin G. · Infants ≥1 month of age identified as having reactive serologic tests for syphilis should be treated with aqueous crystalline penicillin G. · If the child has no clinical manifestations of the disease and the cerebrospinal fluid examination is normal, penicillin G at up to three weekly doses can be considered. · Any child suspected of having congenital syphilis with neurologic involvement should be treated with aqueous crystalline penicillin G. · Infants and children requiring treatment for syphilis who have a history of penicillin allergy or develop an allergic reaction should be desensitized. Urethritis · Azithromycin or doxycycline is recommended. Alternative regimens include erythromycin, levofloxacin or ofloxacin. · In the case of recurrent or persistent urethritis, if the patient was compliant with the initial regimen and re-exposure can be excluded, metronidazole or tinidazole plus azithromycin is recommended. Cervicitis · Azithromycin or doxycycline is recommended. Chlamydia · Azithromycin or doxycycline is recommended. · Alternative agents include erythromycin, levofloxacin or ofloxacin. · Azithromycin or amoxicillin is recommended in pregnant patients. An alternative agent is erythromycin. · Infants with ophthalmia neonatorum should be treated with oral erythromycin. · Infants with pneumonia caused by *Chlamydia trachomatis* should be treated with oral erythromycin. · Children with chlamydial infection should be treated with oral erythromycin (patients weighing <45 kg), azithromycin (patients weighing ≥45 kg and <8 years), or azithromycin or doxycycline (patients ≥8 years of age). Gonococcal infections · Patients infected with *Neisseria gonorrhoeae* are frequently coinfected with *C trachomatis* and should be treated for both infections. · Ceftriaxone is recommended. If ceftriaxone is not an option, other regimens include cefixime or single dose injectable cephalosporin regimens plus azithromycin or doxycycline. · Gonococcal infections of the pharynx should be treated with ceftriaxone plus azithromycin or doxycycline. · Gonococcal conjunctivitis should be treated with ceftriaxone.

Clinical Guideline	Recommendations
	· Disseminated gonococcal infection should be treated with ceftriaxone. Alternative agents include cefotaxime or ceftizoxime. · Gonococcal meningitis and endocarditis should be treated with ceftriaxone. · Ophthalmia neonatorum should be treated with ceftriaxone. · Gonococcal scalp abcesses should be treated with ceftriaxone or cefotaxime. · Infants born to mothers with untreated gonorrhea should be treated with ceftriaxone. · Children weighing >45 kg should be treated with a regimen recommended for adults. · Children weighing ≤45 kg should be treated with ceftriaxone at an appropriate dose. · Ceftriaxone is recommended in children with bacteremia or arthritis. · Erythromycin ophthalmic ointment is recommended as prophylaxis against ophthalmia neonatorum at birth. If erythromycin is not available, infants at risk can be administered ceftriaxone. Bacterial vaginosis · Metronidazole orally or topically or topical clindamycin are recommended. · Alternative agents include oral tinidazole or oral or intravaginal clindamycin. · Intravaginal metronidazole is an option in patients who are unable to tolerate oral metronidazole. · Treatment of all pregnant women with symptoms is recommended. Oral metronidazole or clindamycin is recommended. Trichomoniasis · Oral metronidazole or tinidazole is recommended. Vulvovagnial candidiasis · Over-the-counter butoconazole, clotrimazole, miconazole or tioconazole are recommended. · Prescription agents include butoconazole, nystatin, terconazole or oral fluconazole. · Oral fluconazole weekly for six months is the recommended treatment for recurrent infection. · Severe vulvovaginal candidiasis should be treated with seven to 14 days of topical therapy or fluconazole in two consecutive doses (second dose 72 hours after initial dose). · Only topical therapies are recommended in pregnancy. Pelvic inflammatory disease · Mild to moderate pelvic inflammatory disease should be treated with parenteral or oral therapies. · Recommended parenteral regimen A: cefotetan or cefoxitin plus doxycycline (oral or intravenous). · Recommended parenteral regimen B: clindamycin plus gentamicin. · Alternative parenteral regimens are ampicillin/sulbactam plus doxycycline (oral or intravenous). · Outpatient oral therapy may be considered in patients with mild to

Clinical Guideline	Recommendations
	moderate disease. Recommended regimens include ceftriaxone plus doxycycline with or without metronidazole, cefoxitin and probenecid plus doxycycline with or without metronidazole, or another parenteral 3rd generation cephalosporin plus doxycycline with or without metronidazole. · If parenteral cephalosporin therapy is not feasible, fluoroquinolones with or without metronidazole may be considered if the community prevalence and individual risk for gonorrhea are low. Epididymitis · Ceftriaxone plus doxycycline is recommended. For acute infections most likely caused by enteric organisms, levofloxacin or ofloxacin are recommended. Human papillomavirus · External genital warts: o Podofilox 0.5% solution or gel, imiquimod 5% cream or sinecatechins 15% ointment are recommended as patient-applied treatments. o Cryotherapy with liquid nitrogen or cryoprobe, podophyllin resin, trichloroacetic acid or bichloroacetic acid or surgical removal are recommended as provider-administered treatments. o Alternative regimens include intralesional interferon, photodynamic therapy and topical cidofovir. · Cervical warts: o Biopsy evaluation is recommended to exclude high-grade squamous intraepithelial lesions. · Vaginal warts: o Cryotherapy with liquid nitrogen or trichloroacetic acid or bichloroacetic acid are recommended. · Urethral meatus warts: o Cryotherapy with liquid nitrogen or podophyllin in compound tincture of benzoin is recommended. · Anal warts: o Cryotherapy with liquid nitrogen, trichloroacetic acid or bichloroacetic acid or surgical removal is recommended. Proctitis · Ceftriaxone plus doxycycline is recommended. Pediculosis pubis · Permethrin or pyrethrins are recommended. · Alternative agents include malathion or ivermectin. Scabies · Permethrin or ivermectin are recommended. · Lindane is an alternative agent, not recommended as first-line. Prophylaxis after sexual assault · Hepatitis B vaccination. · Empirical regimen for Chlamydia, gonorrhea and trichomonas. · Emergency contraception.

Clinical Guideline	Recommendations
	· Ceftriaxone or cefixime plus metronidazole plus azithromycin or doxycycline is the recommended regimen.
Infectious Diseases Society of America: **The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America (2006)**[73†]	<u>Early Lyme disease</u> · Doxycycline, amoxicillin or cefuroxime for 10 to 21 days are the preferred treatment options for adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations or advanced atrioventricular heart block. · Children under the age of eight should be treated with amoxicillin or cefuroxime. Children eight years of age and older may be treated with doxycycline. · Macrolides should be reserved for patients who are intolerant to doxycycline, amoxicillin or cefuroxime. · First generation cephalosporins are ineffective and should not be used. · When erythema migrans cannot be differentiated from bacterial cellulitis, it is reasonable to treat with cefuroxime or amoxicillin/clavulanate. · Ceftriaxone is effective but is not “superior” to oral agents and is more likely to cause serious adverse events. · Doxycycline should be avoided in pregnant patients. <u>Lyme meningitis and other manifestations of early neurologic Lyme disease</u> · Ceftriaxone is recommended. · Alternatives include parenteral cefotaxime or penicillin G. · Oral doxycycline may be used in patients intolerant to β-lactams. · Ceftriaxone is recommended in children. An alternative agent is cefotaxime or penicillin G. · Children eight years of age and older may be treated with oral doxycycline. · Antibiotics may not hasten the resolution of seventh cranial nerve palsy associated with Lyme disease but are recommended to prevent further sequelae. <u>Lyme carditis</u> · Patients with atrioventricular heart block and/or myopericarditis may be treated with oral or parenteral antibiotic therapy. · Ceftriaxone is recommended as initial management for hospitalized patients. <u>Borrelial lymphocytoma</u> · Recommended regimens are the same as for erythema migrans. <u>Late Lyme disease with Lyme arthritis</u> · Doxycycline, amoxicillin or cefuroxime are recommended in patients without neurological manifestations. · Children under the age of eight should be treated with amoxicillin or cefuroxime. Children eight years of age and older may be treated with doxycycline. · Adult patients with Lyme arthritis and evidence of neurological manifestations should be treated with parenteral ceftriaxone. Cefotaxime or penicillin G are acceptable alternatives. · Patient with persistent joint swelling may be treated with a second four-week course of oral antibiotics or a two to four week course of

Clinical Guideline	Recommendations
	ceftriaxone. Late neurological Lyme disease · Parenteral ceftriaxone is recommended for adults and children. · Cefotaxime or penicillin G are alternatives. Acrodermatitis chronic atrophicans · Recommended regimens are the same as for erythema migrans. Long-term treatment · Antibiotic therapy is not recommended for patients with long-term (≥6 months) subjective symptoms. Human granulocytic anaplasmosis · Doxycycline is recommended. · Children <8 years of age without concomitant Lyme disease may be treated with an abbreviated course of doxycycline. If the child has concomitant Lyme disease, amoxicillin or cefuroxime are recommended after the course of doxycycline. · In patients not suited for treatment with doxycycline, rifampin is recommended. Patients with concomitant Lyme disease should also be treated with amoxicillin or cefuroxime. Babesiosis · Atovaquone plus azithromycin or clarithromycin plus quinine is recommended. · Clarithromycin plus quinine is recommended in patients with severe disease.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2010)**[74]	Management of exacerbations of Chronic Obstructive Pulmonary Disease (COPD) with a bacterial component · Predominant bacteria include *H influenzae*, *S pneumoniae* and *M catarrhalis*. · Patients with severe COPD requiring mechanical ventilation may be more frequently infected with *P aeruginosa*. · Patients with mild exacerbations and no risk for poor outcome may be treated with oral penicillin, ampicillin, amoxicillin, tetracycline or SMX/TMP. Alternative agents include amoxicillin/clavulanate, a macrolide, a second or third generation cephalosporin or a ketolide. · Patients with moderate exacerbations and risk factors for poor outcomes should be treated with amoxicillin/clavulanate. Alternative agents are fluoroquinolones. Parenteral options include β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones. · Patients with severe exacerbations with risk factors for *P aeruginosa* should be treated with high dose oral or parenteral fluoroquinolones or parenteral β-lactam with *P aeruginosa* activity.
American Heart Association: **Prevention of Infectious Endocarditis (2007)**[75]	· Antibiotic prophylaxis is recommended for patients at the highest risk of adverse outcome from endocarditis, including those with: o Prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Previous infective endocarditis. o Congenital heart disease: § Unrepaired cyanotic congenital heart disease

Clinical Guideline	Recommendations
	including palliative shunts and conduits. § Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure. § Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization). o Cardiac transplantation recipients who develop cardiac valvulopathy. · Antibiotic prophylaxis is no longer recommended based solely on an increased lifetime risk of developing infectious endocarditis. · Antibiotic prophylaxis should be administered as a single dose before the procedure. · Prophylaxis is recommended for all patients described above who are undergoing a dental procedure which involves manipulation of the gingival tissue or the periapical region of the teeth or perforation of the oral mucosa. · Recommended regimens include: o Oral: amoxicillin 2 g (adults) or 50 mg/kg (children). o Unable to take oral medication: ampicillin or ceftriaxone or cefazolin. o Allergic to penicillins or ampicillin, oral: cephalexin or clindamycin or azithromycin or clarithromycin. · Allergic to penicillins or ampicillin and unable to take oral medications: cefazolin or ceftriaxone or clindamycin. · Antibiotic prophylaxis with a regimen described above for patients described above is recommended prior to an invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa such as tonsillectomy and adenoidectomy. · For patients described above who undergo an invasive respiratory tract procedure to treat an established infection it is recommended that the regimen contain an agent effective against *S viridans*. If the infections is known or suspected to be caused by *S aureus* the regimen should include an antistaphylococcal penicillin or cephalosporin or vancomycin in patients who can't tolerate a penicillin. Vancomycin is also recommended if the infection is known or suspected to be caused by MRSA. · The administration of prophylactic antibiotics is no longer recommended solely to prevent endocarditis in patients undergoing a genitourinary or gastrointestinal tract procedure. · Patients described above with infections of the genitourinary or gastrointestinal tract or for those receiving antibiotic therapy to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary tract procedure, the regimen should include an agent active against enterococci, such as penicillin, ampicillin, piperacillin or vancomycin. · For patients described above scheduled for an elective cytoscopy or other urinary tract manipulation who have an enterococcal urinary tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure is reasonable. If the procedure is not

Clinical Guideline	Recommendations
	elective, empiric or specific antimicrobial therapy may be administered to the patient containing an agent active against enterococci. · Amoxicillin or ampicillin is preferred for enterococcal coverage in these patients. Vancomycin may be used in patients unable to tolerate penicillin. · In patients described above who undergo a surgical procedure involving infected skin, skin structure or musculoskeletal tissue, it is reasonable that the therapeutic regimen for the treatment of the infection contain an agent active against staphylococci and β-hemolytic streptococci such as an antistaphylococcal penicillin or a cephalosporin. Vancomycin and clindamycin are options in patients unable to tolerate a β-lactam or who are known or suspected to have an infection caused by a methicillin-resistant staphylococcus.
American Academy of Pediatric Dentistry: **Clinical Guideline on Antibiotic Prophylaxis for Dental Patients at Risk for Infection (2008)**[76]	· Infective endocarditis prophylaxis for dental procedures is reasonable only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis. · For patients with those conditions, prophylaxis is recommended for procedures involving manipulation of gingival tissue or periapical region of teeth or perforation of the oral mucosa. · Prophylaxis is not recommended based solely on an increased lifetime risk of infective endocarditis. · Recommended regimens include: o Oral: amoxicillin 2 g (adults) or 50 mg/kg (children). o Unable to take oral medication: ampicillin or ceftriaxone or cefazolin. o Allergic to penicillins or ampicillin, oral: cephalexin or clindamycin or azithromycin or clarithromycin. o Allerigic to penicillins or ampicillin and unable to take oral medications: cefazolin or ceftriaxone or clindamycin.
Infectious Disease Society of America/ Surgical Infection Society: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[77]	<u>Community-acquired infection of mild to moderate severity in adults</u> · Single agent therapy with ticarcillin/clavulanate, cefoxitin, ertapenem, moxifloxacin or tigecycline or combination therapy of metronidazole with cefazolin, cefuroxime, ceftriaxone, levofloxacin or ciprofloxacin is preferred over regimens with substantial antipseudomonal activity. · Ampicillin/sulbactam, cefotetan and clindamycin are not recommended due to high rates of resistance. · Empiric therapy with antifungals or coverage for Enterococcus is not recommended. · Aminoglycosides are not recommended for routine use because of the risk of toxicity. · Agents recommended for higher severity infections are not recommended for mild to moderate community-acquired infections because of the risk of toxicity and development of resistance. <u>High-risk community-acquired infections in adults</u> · The empiric use of broad-spectrum agents with activity against gram-negative organisms including meropenem, imipenem/cilastatin, doripenem, piperacillin/tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole or ceftazidime or cefepime in combination with metronidazole is recommended. · Aztreonam plus metronidazole with the addition of an agent effective against gram-positive cocci is an alternative.

Clinical Guideline	Recommendations
	· Quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E coli*. · In the absence of evidence of resistant pathogens, aminoglycosides or another second agent effective against gram-negative facultative and anaerobic bacilli and/or agents effective against MRSA should not be used. · Empiric used of agents effective against enterococci is recommended. Health care-associated infection in adults · Multidrug regimens that include agents with expanded spectra of activity against gram-negative facultative and anaerobic bacilli, such as meropenem, imipenem/cilastatin, doripenem, piperacillin/tazobactam or ceftazidime may be required. Therapy should be tailored based on local microbiology results and culture and susceptibility reports when they become available. Antifungal therapy · For patients with severe community-acquired or health care-associated infections with cultures that show Candida, antifungal therapy is recommended. · Fluconazole is an appropriate first-line choice if C albicans is isolated. · For fluconazole resistant Candida species and critically ill patients, an echinocandin (caspofungin, micafungin or anidulafungin) is recommended. · Amphotericin B is not recommended due to its toxicity. Anti-enterococcal therapy · Empiric therapy for enterococci is recommended for patients with health care-associated infections when enterococci are recovered, patients with post-operative infections, patients that have received cephalosporins or other antimicrobial agents selecting for Enterococcus species, immunocompromised patients and patients with valvular heart disease or prosthetic intravascular materials. · Therapy should be directed against *E faecalis* and can include ampicillin/piperacillin and vancomycin. · Empiric therapy for vancomycin-resistant *E faecium* is not recommended unless patient is at very high risk or patient is known to be colonized with *E faecium*. Anti-MRSA therapy · Empiric therapy for MRSA should be provided to patients with health care-associated infections with known colonization with MRSA or are at high risk for MRSA infection because of prior treatment failure and significant antibiotic exposure. · Vancomycin is recommended for treatment if suspected or proven infection due to MRSA. Cholecystitis and cholangitis in adults · For patients with suspected cholecystitis and cholangitis, antibiotic therapy is recommended when a biliary-enteric anastomosis is present. · In community-acquired acute cholecystitis of mild to moderate severity, cefazolin, cefuroxime or ceftriaxone is recommended.

Clinical Guideline	Recommendations
	· In acute cholangitis following bilio-enteric anastomosis of any severity and community-acquired acute cholecystitis of severe physiologic disturbance, advance age or immunocompromised state, a combination regimen with metronidazole and imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, ciprofloxacin, levofloxacin or cefepime is recommended. · For health care-associated biliary infection of any severity, the above regimen (a combination regimen with metronidazole and imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, ciprofloxacin, levofloxacin or cefepime) with the addition of vancomycin is recommended. Pediatric infection · For pediatric patients with complicated intra-abdominal infections, acceptable broad-spectrum regimens include an aminoglycoside based regimen, a carbapenem (imipenem, meropenem, or ertapenem) a β-lactam/β-lactamase inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanate) or an advanced generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime or cefepime) with metronidazole. · For children with severe reactions to β-lactam antibiotics, ciprofloxacin plus metronidazole or an aminoglycoside based regimen are recommended. · In neonates with necrotizing enterocolitis, the broad-spectrum antibiotics that may be useful are ampicillin, gentamicin and metronidazole; ampicillin, cefotaxime and metronidazole; or meropenem. For suspected MRSA, vancomycin may be used in place of ampicillin. If the cultures are consistent with fungal infections, fluconazole and amphotericin should be used.
National Surgical Infection Prevention Project: **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project (2004)**[78]	Sponsoring organizations include the following: American Academy of Orthopaedic Surgeons; American Association of Critical Care Nurses; American Association of Nurse Anesthetists; American College of Surgeons; American College of Osteopathic Surgeons; American Geriatrics Society; American Society of Anesthesiologists; American Society of Colon and Rectal Surgeons; American Society of Health-System Pharmacists; American Society of PeriAnesthesia Nurses; Ascension Health; Association of PeriOperative Registered Nurses; Association for Professionals in Infection Control and Epidemiology; Infectious Diseases Society of America; Medical Letter; Premier; Society for Healthcare Epidemiology of America; Society of Thoracic Surgeons; and Surgical Infection Society. Cardiothoracic and vascular surgery · Intravenous cefazolin or intravenous cefuroxime are recommended. · If the patient has a β-lactam allergy, intravenous vancomycin is appropriate and intravenous clindamycin is an alternative. Colorectal surgery · Oral neomycin plus oral erythromycin or oral neomycin plus oral metronidazole are recommended along with administration of a mechanical bowel preparation. · Intravenous cefotetan or intravenous cefoxitin are recommended for parental prophylaxis. Intravenous cefazolin plus oral metronidazole are recommended as a cost-effective alternative.

Clinical Guideline	Recommendations
	· For patients with a confirmed allergy or adverse reaction to β-lactams, intravenous clindamycin plus intravenous gentamicin, intravenous aztreonam or intravenous ciprofloxacin; intravenous metronidazole plus intravenous gentamicin or intravenous ciprofloxacin are recommended. A single dose of intravenous levofloxacin can be substituted for intravenous ciprofloxacin. Gynecologic and obstetric surgery · Intravenous cefotetan is preferred for abdominal or vaginal hysterectomy. Intravenous cefazolin and intravenous cefoxitin are reasonable alternatives. · Intravenous metronidazole is an alternative, but may be less effective as monotherapy. · For patients with a β-lactam allergy, intravenous clindamycin plus intravenous gentamicin, intravenous aztreonam or intravenous ciprofloxacin; intravenous metronidazole plus intravenous gentamicin or intravenous ciprofloxacin; or intravenous clindamycin monotherapy are recommended. A single dose of intravenous levofloxacin can be substituted for intravenous ciprofloxacin.

*Agent not currently available in the United States.
†The 2006 Lyme disease guidelines by the Infectious Disease Society of America were the subject of an antitrust investigation by the Connecticut Attorney General in 2006 to examine potential conflicts of interest among panelist and whether the panelist failed to consider divergent medical opinion. An independent review panel was convened and, in 2010, agreed that no changes needed to be made to the 2006 guidelines.

Conclusions

The third generation cephalosporins are used to treat a variety of infections caused by susceptible organisms including skin and skin structure infections, genitourinary tract infections and respiratory tract infections. Third generation cephalosporins are active against streptococci, *Haemophilus influenza* and *Moraxella catarrhalis* and are more active against gram-negative bacilli compared to other cephalosporins.[2,3] They are not as active against susceptible strains of staphylococci as compared to first generation cephalosporins. Treatment guidelines identify third generation cephalosporins as alternative empiric agents for the treatment of community-acquired pneumonia, and as treatment options for infections due to *Enterobacteriaceae*.[59,60] They are considered alternative agents for the treatment of otitis media in patients with non-type 1 penicillin allergies and second-line agents for the treatment of sinusitis due to penicillin and sulfamethoxazole/trimethoprim resistant bacteria or in patients with non-type 1 penicillin allergies.[62,66] Cefixime is considered a second-line agent for the treatment of gonorrhea after ceftriaxone.[72] The Global Initiative for Chronic Obstructive Lung Disease recommends the use a second or third generation cephalosporin as an alternative to penicillin, ampicillin, amoxicillin, tetracycline or sulfamethoxazole/trimethoprim in patients with chronic obstructive pulmonary disease and mild exacerbations with no risk of a poor outcome.[74]

Clinical trials evaluating the third generation cephalosporins for the treatment of acute exacerbations of chronic bronchitis have not consistently demonstrate significant differences in clinical response or eradication rate when compared to other cephalosporins.[13-18] Verghese and colleagues compared cefixime and cephalexin in the treatment of hospitalized patients with exacerbations of chronic bronchitis and demonstrated significantly better clinical cure rates in patients treated with cefixime compared to cephalexin, though diarrhea occurred more commonly in the cefixime group.[19] Cefixime and cefpodoxime have been shown to be effective in the treatment of gonorrhea in open-label and dose-response studies, and cefixime has been shown to have comparable efficacy when compared to ceftriaxone.[20-24] Asmar et al. compared cefixime and cefpodoxime in the treatment of acute otitis media. No significant differences were observed between agents in clinical or microbiological cure rates.[25] Studies evaluating the use of

the third generation cephalosporins for the treatment of pharyngitis and/or tonsillitis have failed to consistently demonstrate “superiority” of any third generation cephalosporin over penicillin or amoxicillin.[26-33] In the treatment of lower respiratory tract infections including community-acquired pneumonia, no consistently significant differences were observed when the third generation cephalosporins were compared with each other or with cephalosporins in other generations.[34-36] Studies evaluating the treatment of skin and soft tissue infections, sinusitis and urinary tract infections did not consistently demonstrate the “superiority” of any third generation cephalosporin when compared with in-class or with other cephalosporins in other generations.[37-43]

All third generation cephalosporins are available generically in at least one dosage form or strength with the exception of cefixime (Suprax®) and ceftibuten (Cedax®).

References

1. Calderwood S. Overview of the beta-lactam antibiotics. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2010 [cited 2012 Jul 31]. Available from: http://www.utdol.com/utd/index.do.
2. Calderwod S. Cephalosporins. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2010 [cited 2012 Jul 31]. Available from: http://www.utdol.com/utd/idex.do.
3. Antiinfectives 8:00, Antibacterials 8:12, Cephalosporins 8:12.06. In: McEvoy GK ed. American Hospital Formulary Services, AHFS Drug Information 2011 [monograph on the internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2011 [cited 2012 Jul 31]. Available from: http://online.statref.com.
4. Cefdinir capsules [package insert]. Sellersville (PA): Teva Pharmaceuticals USA; 2009 Jan.
5. Cefdinir powder for suspension [package insert]. Sellersville (PA): Teva Pharmaceuticals USA; 2009 Jun.
6. Spectracef® tablets [package insert]. Cary (NC): Cornerstone Therapeutics Inc.; 2009.
7. Cefditoren tablets [package insert]. Cary (NC): Aristos Pharmaceuticals, Inc.; 2009 Jul.
8. Suprax® [package insert]. Baltimore (MD): Lupin Pharmaceuticals Inc.; 2008 Oct.
9. Cefpodoxime tablets [package insert]. Dayton (NJ): Aurobindo Pharma USA, Inc.; 2008 Feb.
10. Cefpodoxime granule for suspension [package insert]. Princeton (NJ): Sandoz Inc.; 2008 Sept.
11. Cedax® [package insert]. Gonzales (LA): Pernix Therapeutics, LLC; 2010 Apr.
12. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2011 [cited 2012 Jul 31]. Available from: http://www.thomsonhc.com/.
13. Phillips H, Van Hook CJ, Butler T, et al. A comparison of cefpodoxime proxetil and cefaclor in the treatment of acute exacerbation of COPD in adults. Chest. 1993;104(5):1387-91.
14. Chirurgi VA, Edelstein H, Oster SE, et al. Ceftibuten versus cefaclor for the treatment of bronchitis. J Antimicrob Chemother. 1991;28:577-80.
15. Fogarty CM, Bettis RB, Griffin TJ, Keyserling CH, Nemeth MA, Tack KJ. Comparison of a 5 day regimen of cefdinir with a 10 day regimen of cefprozil for treatment of acute exacerbation of chronic bronchitis. J Antimicrob Chemother. 2000;45:851-8.
16. Van Herwaarden C, Langan C, Siemon G, Rudolph C, Keyserling C, Nemeth M, et al. International study comparing cefdinir and cefuroxime axetil in the treatment of patients with acute exacerbation of chronic bronchitis. Int J Infect Dis. 1999;4:26-33.
17. Alvarez-Sala JL, Kardos P, Martínez-Beltrán J, Coronel P, Aguilar L. Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. Antimicrob Agents Chemothera. 2006;50(5):1762-7.
18. Zuck P, Petitpretz P, Geslin P, Rio Y, Leblanc F. Bacteriological eradication of streptococcus pneumoniae from patients with acute exacerbations of chronic bronchitis: cefuroxime axetil versus cefixime. Int J Clin Prac. 1999;53(6):437-43.
19. Verghese A, Roberson D, Kalbfleisch JH, Sarubbi F. Randomized comparative study of cefixime versus cephalexin in acute bacterial exacerbations of chronic bronchitis. Antimicrob Agents Chemother. 1990;34(6):1041-4.
20. Handsfield H, McCormack W, Hook E, Douglas J, Covino J, Verdon M, et al. A comparison of single-dose cefixime with ceftriaxone as a treatment for uncomplicated gonorrhea. NEJM. 1991;325(19):1337-41.
21. Verdon M, Douglas J, Wiggins S, Handfield H. Treatment of uncomplicated gonorrhea with single doses of 200 mg cefixime. Sexually Transmitted Diseases. 1993;20(5):290-3.
22. Plourde P, Tyndall M, Agoki E, Ombette J, Slaney L, D'Costa L, et al. Single-dose cefixime versus single-dose ceftriaxone in the treatment of antimicrobial resistant Neisseria gonorrhoeae infection. Journal of Infectious Diseases. 1992;166(4):919-22.
23. Portilla I, Lutz B, Montalvo M, Mogabag W. Oral cefixime versus intramuscular ceftriaxone in patients with uncomplicated gonococcal infections. Sexually Transmitted Diseases. 1992;19(2):94-8.
24. Novak E, Paxton L, Tubbs H, Turner L, Keck C, Yatsu J. Orally administered cefpodoxime proxetil for treatment of uncomplicated gonococcal urethritis in males: a dose-response study. Antimicrobial agents and Chemotherapy. 1992;1764-5.

25. Asmar BI, Dajani AS, Del Beccaro MA, Mendelman PM. Comparison of cefpodoxime proxetil and cefixime in the treatment of acute otitis media in infants and children. Pediatrics. 1994;94(6):847-52.
26. Nemeth M, McCarty J, Gooch H, Henry D, Keyserling C, Tack K. Comparison of cefdinir and penicillin for the treatment of streptococcal pharyngitis. Clinical Therapeutics. 1999;21(11):1873-81.
27. Tack K, Henry D, Gooch W, Brink D, Keyserling C and the Cefdinir Pharyngitis Study Group. Five-day cefdinir treatment for streptococcal pharyngitis. Antimicrobial Agents and Chemotherapy. 1998;42(5):1073-5.
28. Brook I. A pooled comparison of cefdinir and penicillin in the treatment of group A beta-hemolytic streptococcal pharyngotonsillitis. Clin Therap. 2005;27(8):1266-73.
29. Ozaki T, Nishimura N, Suzuki M, Narita A, Watanabe N, Ahn J, et al. Five-day oral cefditoren pivoxil versus 10-day oral amoxicillin for pediatric group A streptococcal pharyngotonsillitis. J Infect Chemother. 2008;14:213-8.
30. Block S, Hedrick J, Tyler R. Comparative study of the effectiveness of cefixime and penicillin V for the treatment of streptococcal pharyngitis in children and adolescents. Pediatr Infect Dis J. 1992;11:919-25.
31. Adam D, Cefixime Study Group, Hostalek U, Troster K. 5-day cefixime therapy for bacterial pharyngitis and/or tonsillitis: comparison with 10-day penicillin V therapy. Infection. 1995;23(Suppl 2):S83-6.
32. Pichichero ME, Gooch WM, Rodriguez W, Blumer JL, Aronoff SC, Jacobs RF, et al. Effective short-course treatment of acute group A beta-hemolytic streptococcal tonsillopharyngitis. Arch Pediatr Adolesc Med. 1994;148:1053-60.
33. Pichichero M, McLinn S, Gooch M, Rodriguez M, Goldfarb J, Reidenberg B, et al. Ceftibuten vs. penicillin V in group A beta-hemolytic streptococcal pharyngitis. Pediatr Infect Dis J. 1995;14:S102-7.
34. van Zyle L, le Roux J, LaFata J, Volk R, Palo W, Flamm R, et al. Cefditoren pivoxil versus cefpodoxime proxetil for community-acquired pneumonia: results from a multi-center, prospective, randomized, double-blind study. Clin Therap. 2002;24(11):1840-53.
35. Drehobl M, Bianchi P, Keyserling CH, Tack KJ, Griffin TJ. Comparison of cefdinir and cefaclor in the treatment of community-acquired pneumonia. Antimicrob Agents Chemother. 1997;41(7):1579-83.
36. Sengupta J, Mondal AK, Jain P, Garg RD, Mathur NC, Moharana AK. Comparative evaluations of cefpodoxime versus cefixime in children with lower respiratory tract infections. Indian J Pediatr. 2004;71(6):517-21.
37. Tack KJ, Keyserling CH, McCarty J, Hedrick JA. Study of use of cefdinir versus cephalexin for treatment of skin infections in pediatric patients. Antimicrob Agents and Chemother. 1997;41(4):739-42.
38. Tack K, Littlejohn T, Mailloux G, Wolf M, Keyserling C. Cefdinir versus cephalexin for the treatment of skin and skin structure infections. Clin Therap. 1998;20(2):244-56.
39. Stevens DL, Pien F, Drehobol M. Comparison of oral cefpodoxime proxetil and cefaclor in the treatment of skin and soft tissue infections. Diagn Microbiol Infect Dis. 1993;16:123-9.
40. Bucko AD, Hunt BJ, Kidd SL, Hom R. Randomized, double-blind, multicenter comparison of oral cefditoren 200 or 400 mg BID with either cefuroxime 250 mg BID or cefadroxil 500 mg BID for the treatment of uncomplicated skin and skin-structure infections. Clin Ther. 2002;27(7):1134-47.
41. Gehanno P, Depondt J, Barry B, Simonet M, Dewever H. Comparison of cefpodoxime proxetil with cefaclor in the treatment of sinusitis. J Antimicrob Chemother. 1990;26(Suppl E): 87-91.
42. Leigh AP, Nemeth MA, Keyserling CH, Hotary LH, Tack KJ. Cefdinir versus cefaclor in the treatment of uncomplicated urinary tract infection. Clin Ther. 2000;22(7):818-25.
43. Ho MW, Wang FD, Fung CP, Liu CY. Comparative study of ceftibuten and cefixime in the treatment of complicated urinary tract infections. J Microbiol Immunol Infect. 2001;34:185-9.
44. Ziering W, McElvaine P. Randomized comparison of once-daily ceftibuten and twice daily clarithromycin in the treatment of acute exacerbations of chronic bronchitis. Infection 1998;26(1):68-75.
45. Martin DH, Sargent SJ, Wendel GD Jr, McCormack WM, Spier NA, Johnson RB. Comparison of azithromycin and ceftriaxone for the treatment of chancroid. Clin Infect Dis. 1995;21:409-14.
46. French LM, Smaill FM. Antibiotic regimens for endometritis after delivery. Cochrane Database Syst Rev. 2004;18(4):CD001067.

47. Piippo T, Stefansson S, Pitkäjärvi T, Lundberg C. Double-blind comparison of cefixime and cefaclor in the treatment of acute otitis media in children. Scand J Infect Dis. 1991;23:459-65.
48. MacLoughlin GJ, Barreto DG, de la Torre C, Pinetta EA, del Castillo F, Palma L. Cefpodoxime proxetil suspension compared with cefaclor suspension for treatment of acute otitis media in pediatric patients. J Antimicrob Chemother. 1996;37:565-73.
49. Blumer JL, McLinn SE, Deabate A, et al. Multinational multicenter controlled trial comparing ceftibuten with cefaclor for the treatment of acute otitis media. Pediatr Infect Dis J. 1995;14:S115-20.
50. Blumer JL, Mclinn SE, Deabate CA, Kafetzis DA, Perrotta RJ, Salgado O. Five-day cefdinir course vs ten-day cefprozil course for treatment of acute otitis media. Pediatr Infect Dis J. 2000;19(12):S147-S52.
51. Block S, Cifaldi M, Gu Y, Paris M. A comparison of 5 days of therapy with cefdinir or azithromycin in children with acute otitis media: a multicenter, prospective single-blind study. Clin Therap. 2005;27(6):786-94.
52. Mandel E, Rockette H, Paradise J, Bluestone C, Nozza R. Comparative efficacy of erythromycin-sulfisoxazole, cefaclor, amoxicillin or placebo for otitis media with effusion on children. Pediatr Infect Dis J. 1991;10:899-906.
53. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. Br J Surg. 1998 Sep;85(9):1232-41.
54. Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD007182
55. Bocquet N, Sergent Alaoui A, Jais JP, Gajdos V, Guigonis V, Lacour B, et al. Randomized trial of oral versus sequential IV/oral antibiotic for acute pyelonephritis in children. Pediatrics. 2012 Feb;129(2):e269-75.
56. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA. 2012 Feb 8;307(6):583-9.
57. Falagas ME, Siempos II, Vardakas KZ. Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomized controlled trials. Lancet Infect Dis. 2008 Jan;8(1):53-66.
58. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2011 [cited 2012 Jul 31]. Available from: http://online.factsandcomparisons.com.
59. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
60. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest. 2005 May;127(5):1752-63.
61. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005 Feb 15;171(4):388-416.
62. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004 May;113(5):1451-65.
63. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis. 2002;35(2):113-25.
64. Gerber M, Baltimore R, Eaton C, Gewitz M, Rowley A, Shulman S et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcus pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality Care and Outcomes Research: Endorsed by the American Academy of Pediatrics. Circulation. 2009;119:1541-51.
65. Institute for Clinical Systems Improvement. Health care guideline: diagnosis and treatment of respiratory illness in children and adults [guideline on the internet]. 3rd ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2011 Jan [cited 2012 Jul 31]. Available from:

http://www.icsi.org/guidelines_and_more/gl_os_prot/respiratory/respiratory_illness_in_children_and_adults__guideline_/respiratory_illness_in_children_and_adults__guideline__13110.html.
66. American Academy of Pediatrics. Clinical practice guidelines: management of sinusitis. Pediatrics. 2001;108(3):798-808.
67. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitley RJ. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004 Nov 1;39(9):1267-84.
68. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
69. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012 Jun;54(12):e132-73.
70. American College of Obstetricians and Gynecologists Practice Bulletin: Treatment of urinary tract infections in nonpregnant women. Obstetrics and Gynecology. 2008;111(3):785-94.
71. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al.; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. 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 Mar;52(5):e103-20.
72. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR Morb Mortal Wkly Rep. 2010;59(No. RR-12):1-116. Available from: http://www.cdc.gov/std/treatment/2010/. Accessed Jul 31, 2012.
73. Wormser G, Dattwyler R, Shapiro E, Halperin J, Steere A, Klempner M. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines from the Infectious Diseases Society of America. Clinical Infectious Diseases. 2006;43:1089-134.
74. Rodriguez-Roisin R, Anzueto A, Bourbeau J, deGuia T, Hui D, Jenkins C, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2010). [guideline on the internet]. Global Initiative for Chronic Obstructive Lung Disease, Inc.; 2010 [cited 2012 Jul 31]. Available from: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html.
75. Wilson W, Taubert K, Gewitz M, Lockhart P, Baddour L, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736-54.
76. American Academy of Pediatric Dentistry (AAPD). Guideline on antibiotic prophylaxis for dental patients at risk for infection. Chicago (IL): American Academy of Pediatric Dentistry (AAPD); 2008.
77. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt). 2010 Feb;11(1):79-109.
78. Bratzler DW, Houck PM; Surgical Infection Prevention Guidelines Writers Workgroup; Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004 Jun 15;38(12):1706-15.