Key References

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1. Heffron R. *Pneumonia, With Special Reference to Pneumococcus Lobar Pneumonia*. Cambridge, MA: Harvard University Press; 1938. (reprinted 1979).
8. Avery OT, MacLeod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types: induction of transformation by a deoxyrigonucleic acid fraction from pneumococcus type 3. *J Exp Med*. 1944;79:137–158.
18. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet*. 2009;374:893–902.
20. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373:415–427.
21. Centers for Disease Control and Prevention. ABCs Report: *Streptococcus pneumoniae*; 2016. https://www.cdc.gov/abcs/reports-findings/survreports/spneu16.html. Accessed March 1, 2018.
27. Rubins JB, Alter M, Loch J, et al. Determination of antibody responses of elderly adults to all 23 capsular polysaccharides after pneumococcal vaccination. *Infect Immun*. 1999;67:5979–5984.
28. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. *Clin Infect Dis*. 2017;65:1806–1812.
30. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*. 2015;372:1114–1125.
33. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. *Ann Intern Med*. 1964;60:759–776.
34. Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. *Medicine (Baltimore)*. 2000;79:210–221.
35. Kyaw MH, Rose CE Jr, Fry AM, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. *J Infect Dis*. 2005;192:377–386.
50. Watt JP, O'Brien KL, Benin AL, et al. Invasive pneumococcal disease among Navajo adults, 1989-1998. *Clin Infect Dis*. 2004;38:496–501.
69. Weiser JN, Ferreira DM, Paton JC. *Streptococcus pneumoniae*: transmission, colonization and invasion. *Nat Rev Microbiol*. 2018;16:355–367.
70. Cremers AJ, Zomer AL, Gritzfeld JF, et al. The adult nasopharyngeal microbiome as a determinant of pneumococcal acquisition. *Microbiome*. 2014;2:44.
81. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clin Infect Dis*. 2010;51:692–699.
82. Alanee SRJ, McGee L, Jackson D, et al. Association of serotypes of *Streptococcus pneumoniae* with disease severity and outcome in adults: an international study. *Clin Infect Dis*. 2007;45:46–51.
87. Dagan R, Givon-Lavi N, Zamir O, et al. Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. *J Infect Dis*. 2002;185:927–936.
88. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348:1737–1746.
90. Malley R, Trzcinski K, Srivastava A, et al. CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. *Proc Natl Acad Sci USA*. 2005;102:4848–4853.
109. Lipsitch M, Whitney CG, Zell E, et al. Are anticapsular antibodies the primary mechanism of protection against invasive pneumococcal disease? *PLoS Med*. 2005;2:e15.
117. Siber GR. Pneumococcal disease: prospects for a new generation of vaccines. *Science*. 1994;265:1385–1387.
118. Snapper CM. Differential regulation of protein- and polysaccharide-specific Ig isotype production in vivo in response to intact *Streptococcus pneumoniae*. *Curr Protein Pept Sci*. 2006;7:295–305.
152. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis*. 2008;198:962–970.
157. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. *N Engl J Med*. 1995;333:845–851.
159. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
177. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. 2000;355:2106–2111.
290. Nie W, Li B, Xiu Q. Beta-Lactam/macrolide dual therapy versus beta-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69:1441–1446.
296. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347:1549–1556.
300. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J*. 2000;19:187–195.
302. Musher DM, Groover JE, Rowland JM, et al. Antibody to capsular polysaccharides of *Streptococcus pneumoniae*: prevalence, persistence, and response to revaccination. *Clin Infect Dis*. 1993;17:66–73.
309. O'Brien KL, Hochman M, Goldblatt D. Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness an issue? *Lancet Infect Dis*. 2007;7:597–606.
311. de Roux A, Schmoele-Thoma B, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. *Clin Infect Dis*. 2008;46:1015–1023.
314. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005;365:1139–1146.
326. Austrian R, Douglas RM, Schiffman G, et al. Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Physicians*. 1976;89:184–194.
329. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med*. 1991;325:1453–1460.
341. Maruyama T, Taguchi O, Niederman MS, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. *BMJ*. 2010;340:c1004.
346. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis*. 2015;15:301–309.
358. Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of the 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:1–19.
359. Tomczyk S, Bennett NM, Stoecker C, et al. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63:822–825.

References

1. Heffron R. *Pneumonia, With Special Reference to Pneumococcus Lobar Pneumonia*. Cambridge, MA: Harvard University Press; 1938. (reprinted 1979).
2. Musher DM, Watson DA, Dominguez EA. Pneumococcal vaccination: work to date and future prospects. *Am J Med Sci*. 1990;300:45–52.
3. Heidelberger M, Avery OT. The soluble specific substance of pneumococcus. *J Exp Med*. 1923;38:73–79.
4. Felton LD. Studies on the immunizing substances in pneumococci. *J Immunol*. 1934;27:379–393.
5. Smillie WG, Wornock GH, White HJ. A study of a type I pneumococcus epidemic at the State Hospital at Worcester, Mass. *Am J Public Health Nations Health*. 1938;28:293–302.
6. MacLeod CM, Hodges RG, Heidelberger M, et al. Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. *J Exp Med*. 1945;82:445–465.
7. Griffith F. The significance of pneumococcal types. *J Hyg (Lond)*. 1928;27:113–159.
8. Avery OT, MacLeod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types: induction of transformation by a deoxyrigonucleic acid fraction from pneumococcus type 3. *J Exp Med*. 1944;79:137–158.
9. Sorensen UB. Pneumococcal polysaccharide antigens: capsules and C-polysaccharide. An immunochemical study. *Dan Med Bull*. 1995;42:47–53.
10. Martin M, Turco JH, Zegans ME, et al. An outbreak of conjunctivitis due to atypical *Streptococcus pneumoniae*. *N Engl J Med*. 2003;348:1112–1121.
11. Geno KA, Gilbert GL, Song JY, et al. Pneumococcal capsules and their types: past, present, and future. *Clin Microbiol Rev*. 2015;28:871–899.
12. Morona JK, Morona R, Paton JC. Molecular and genetic characterization of the capsule biosynthesis locus of *Streptococcus pneumoniae* type 19B. *J Bacteriol*. 1997;179:4953–4958.
13. Yother J, Bentley S, Hennessey J Jr. Genetics, biosynthesis and chemistry of pneumococcal capsular polysaccharides. In: Siber G, Klugman KP, Makela P, eds. *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*. Washington, DC: American Society for Microbiology Press; 2008:33–46.
14. Peterson S, Cline RT, Tettelin H, et al. Gene expression analysis of the *Streptococcus pneumoniae* competence regulons by use of DNA microarrays. *J Bacteriol*. 2000;182:6192–6202.
15. Coffey TJ, Enright MC, Daniels M, et al. Recombinational exchanges at the capsular polysaccharide biosynthetic locus lead to frequent serotype changes among natural isolates of *Streptococcus pneumoniae*. *Mol Microbiol*. 1998;27:73–83.
16. Dowson CG. What is a pneumococcus? In: Tuomanen EI, Mitchell TJ, Morrison DA, et al, eds. *The Pneumococcus*. Washington, DC: American Society for Microbiology Press; 2004:3–14.
17. Croucher NJ, Harris SR, Fraser C, et al. Rapid pneumococcal evolution in response to clinical interventions. *Science*. 2011;331:430–434.
18. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet*. 2009;374:893–902.
19. Scott JA, Hall AJ, Muyodi C, et al. Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya. *Lancet*. 2000;355:1225–1230.
20. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373:415–427.
21. Centers for Disease Control and Prevention. ABCs Report: *Streptococcus pneumoniae;* 2010. http://www.cdc.gov/abcs/reports-findings/survreports/spneu10.html. Accessed March 25, 2014.
22. Breiman RF, Spika JS, Navarro VJ, et al. Pneumococcal bacteremia in Charleston County, South Carolina: a decade later. *Arch Intern Med*. 1990;150:1401–1405.
23. Burman LÅ, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors, and prognosis. *Rev Infect Dis*. 1985;7:133–142.
24. Janoff EN, Rubins JB. *Invasive Pneumococcal Disease in Immunocompromised Patients*. Larchmont, NY: Mary Ann Liebert; 2000.
25. Madhi S, Pelton S. Epidemiology, diagnosis, and treatment of serious pneumococcal infections in children. In: Siber G, Klugman KP, Makela P, eds. *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*. Washington, DC: American Society for Microbiology Press; 2008:95–166.
26. Musher DM, Groover JE, Watson DA, et al. Genetic regulation of the capacity to make immunoglobulin G to pneumococcal capsular polysaccharides. *J Investig Med*. 1997;45:57–68.
27. Rubins JB, Alter M, Loch J, et al. Determination of antibody responses of elderly adults to all 23 capsular polysaccharides after pneumococcal vaccination. *Infect Immun*. 1999;67:5979–5984.
28. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. *Clin Infect Dis*. 2017;65:1806–1812.
29. McLaughlin JM, Jiang Q, Isturiz RE, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against hospitalization for community-acquired pneumonia in older US adults: a test-negative design. *Clin Infect Dis*. 2018.
30. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*. 2015;372:1114–1125.
31. Rubins JB, Boulware D, Janoff EN. Pneumococcal pneumonia in adults: epidemiology, clinical features, diagnosis, and therapy. In: Siber G, Klugman KP, Makela P, eds. *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*. Washington, DC: American Society for Microbiology Press; 2008:117–138.
32. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997. *Am J Public Health*. 2000;90:223–229.
33. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. *Ann Intern Med*. 1964;60:759–776.
34. Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. *Medicine (Baltimore)*. 2000;79:210–221.
35. Kyaw MH, Rose CE Jr, Fry AM, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. *J Infect Dis*. 2005;192:377–386.
36. Jackson LA, Janoff EN. Pneumococcal vaccination of elderly adults: new paradigms for protection. *Clin Infect Dis*. 2008;47:1328–1338.
37. Janoff EN, Rubins JB. Immunodeficiency and invasive pneumococcal disease. In: Tuomanen EI, Mitchell TJ, Morrison DA, et al, eds. *The Pneumococcus*. Washington, DC: American Society for Microbiology Press; 2004:252–280.
38. Musher DM. How contagious are common respiratory tract infections? *N Engl J Med*. 2003;348:1256–1266.
39. Henderson FW, Gilligan PH, Wait K, et al. Nasopharyngeal carriage of antibiotic-resistant pneumococci by children in group day care. *J Infect Dis*. 1988;157:256–263.
40. Rauch AM, O'Ryan M, Van R, et al. Invasive disease due to multiply resistant *Streptococcus pneumoniae* in a Houston, Tex, day care center. *Am J Dis Child*. 1990;144:923–927.
41. Gessner BD, Mueller JE, Yaro S. African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. *BMC Infect Dis*. 2010;10:22.
42. Romney MG, Hull MW, Gustafson R, et al. Large community outbreak of *Streptococcus pneumoniae* serotype 5 invasive infection in an impoverished, urban population. *Clin Infect Dis*. 2008;47:768–774.
43. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. *Lancet Infect Dis*. 2005;5:83–93.
44. Hodges R, MacLeod C. Epidemic pneumococcal pneumonia: I. Description of the epidemic. *Am J Hyg*. 1946;44:183–192.
45. Hoge CW, Reichler MR, Dominguez EA, et al. An epidemic of pneumococcal disease in an overcrowded, inadequately ventilated jail. *N Engl J Med*. 1994;331:643–648.
46. Mercat A, Nguyen J, Dautzenberg B. An outbreak of pneumococcal pneumonia in two men's shelters. *Chest*. 1991;99:147–151.
47. Gleich S, Morad Y, Echague R, et al. *Streptococcus pneumoniae* serotype 4 outbreak in a home for the aged: report and review of recent outbreaks. *Infect Control Hosp Epidemiol*. 2000;21:711–717.
48. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med*. 2000;342:681–689.
49. Harrison LH, Dwyer DM, Billmann L, et al. Invasive pneumococcal infection in Baltimore, Md: implications for immunization policy. *Arch Intern Med*. 2000;160:89–94.
50. Watt JP, O'Brien KL, Benin AL, et al. Invasive pneumococcal disease among Navajo adults, 1989-1998. *Clin Infect Dis*. 2004;38:496–501.
51. Watt JP, O'Brien KL, Benin AL, et al. Risk factors for invasive pneumococcal disease among Navajo adults. *Am J Epidemiol*. 2007;166:1080–1087.
52. Davidson M, Parkinson AJ, Bulkow LR, et al. The epidemiology of invasive pneumococcal disease in Alaska, 1986-90: ethnic differences and opportunities for prevention. *J Infect Dis*. 1994;170:368–376.
53. Torzillo PJ, Hanna JN, Morey F, et al. Invasive pneumococcal disease in central Australia. *Med J Aust*. 1995;162:182–186.
54. Huang SS, Finkelstein JA, Rifas-Shiman SL, et al. Community-level predictors of pneumococcal carriage and resistance in young children. *Am J Epidemiol*. 2004;159:645–654.
55. Frenck RW Jr, Glezen WP. Respiratory tract infections in children in day care. *Semin Pediatr Infect Dis*. 1990;1:234–244.
56. Gray BM, Converse GM 3rd, Dillon HC Jr. Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. *J Infect Dis*. 1980;142:923–933.
57. Dowell SF, Whitney CG, Wright C, et al. Seasonal patterns of invasive pneumococcal disease. *Emerg Infect Dis*. 2003;9:573–579.
58. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. *Clin Infect Dis*. 1996;22:100–106.
59. Lowen AC, Mubareka S, Steel J, et al. Influenza virus transmission is dependent on relative humidity and temperature. *PLoS Pathog*. 2007;3:1470–1476.
60. Faden H, Duffy L, Wasielewski R, et al. Relationship between nasopharyngeal colonization and the development of otitis media in children. Tonawanda/Williamsville Pediatrics. *J Infect Dis*. 1997;175:1440–1445.
61. Benin AL, O'Brien KL, Watt JP, et al. Effectiveness of the 23-valent polysaccharide vaccine against invasive pneumococcal disease in Navajo adults. *J Infect Dis*. 2003;188:81–89.
62. Frank DN, Zhu W, Sartor RB, et al. Investigating the biological and clinical significance of human dysbioses. *Trends Microbiol*. 2011;19:427–434.
63. Ekdahl K, Ahlinder I, Hansson HB, et al. Duration of nasopharyngeal carriage of penicillin-resistant *Streptococcus pneumoniae:* experiences from the South Swedish Pneumococcal Intervention Project. *Clin Infect Dis*. 1997;25:1113–1117.
64. Bogaert D, De Groot R, Hermans PW. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis*. 2004;4:144–154.
65. Hodges RG, MacLeod CM, Bernhard WG. Epidemic pneumococcal pneumonia. III. Pneumococcal carrier studies. *Am J Hyg*. 1946;44:207–230.
66. Roy CJ, Milton DK. Airborne transmission of communicable infection—the elusive pathway. *N Engl J Med*. 2004;350:1710–1712.
67. Levine H, Balicer RD, Zarka S, et al. Dynamics of pneumococcal acquisition and carriage in young adults during training in confined settings in Israel. *PLoS ONE*. 2012;7:e46491.
68. Weiser JN. The pneumococcus: why a commensal misbehaves. *J Mol Med*. 2010;88:97–102.
69. Weiser JN, Ferreira DM, Paton JC. *Streptococcus pneumoniae:* transmission, colonization and invasion. *Nat Rev Microbiol*. 2018;16:355–367.
70. Cremers AJ, Zomer AL, Gritzfeld JF, et al. The adult nasopharyngeal microbiome as a determinant of pneumococcal acquisition. *Microbiome*. 2014;2:44.
71. Dorrington MG, Roche AM, Chauvin SE, et al. MARCO is required for TLR2- and Nod2-mediated responses to *Streptococcus pneumoniae* and clearance of pneumococcal colonization in the murine nasopharynx. *J Immunol*. 2013;190:250–258.
72. Malley R, Henneke P, Morse SC, et al. Recognition of pneumolysin by Toll-like receptor 4 confers resistance to pneumococcal infection. *Proc Natl Acad Sci USA*. 2003;100:1966–1971.
73. Weiser JN, Bae D, Fasching C, et al. Antibody-enhanced pneumococcal adherence requires IgA1 protease. *Proc Natl Acad Sci USA*. 2003;100:4215–4220.
74. Musher DM, Groover JE, Reichler MR, et al. Emergence of antibody to capsular polysaccharides of *Streptococcus pneumoniae* during outbreaks of pneumonia: association with nasopharyngeal colonization. *Clin Infect Dis*. 1997;24:441–446.
75. Briles DE, Crain MJ, Gray BM, et al. Strong association between capsular type and virulence for mice among human isolates of *Streptococcus pneumoniae*. *Infect Immun*. 1992;60:111–116.
76. Brueggemann AB, Griffiths DT, Meats E, et al. Clonal relationships between invasive and carriage *Streptococcus pneumoniae* and serotype- and clone-specific differences in invasive disease potential. *J Infect Dis*. 2003;187:1424–1432.

77. Crook DW. Capsular type and the pneumococcal human host-parasite relationship. *Clin Infect Dis*. 2006;42:460–462.
78. Sjostrom K, Spindler C, Ortqvist A, et al. Clonal and capsular types decide whether pneumococci will act as a primary or opportunistic pathogen. *Clin Infect Dis*. 2006;42:451–459.
79. Hausdorff WP, Bryant J, Paradiso PR, et al. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin Infect Dis*. 2000;30:100–121.
80. Bhutta ZA, Das JK, Walker N, et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet*. 2013;381:1417–1429.
81. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clin Infect Dis*. 2010;51:692–699.
82. Alanee SRJ, McGee L, Jackson D, et al. Association of serotypes of *Streptococcus pneumoniae* with disease severity and outcome in adults: an international study. *Clin Infect Dis*. 2007;45:46–51.
83. Weiser JN, Kapoor M. Effect of intrastrain variation in the amount of capsular polysaccharide on genetic transformation of *Streptococcus pneumoniae*: implications for virulence studies of encapsulated strains. *Infect Immun*. 1999;67:3690–3692.
84. Dockrell DH, Whyte MK, Mitchell TJ. Pneumococcal pneumonia: mechanisms of infection and resolution. *Chest*. 2012;142:482–491.
85. Weisholtz SJ, Hartman BJ, Roberts RB. Effect of underlying disease and age on pneumococcal serotype distribution. *Am J Med*. 1983;75:199–205.
86. Lakshman R, Murdoch C, Race G, et al. Pneumococcal nasopharyngeal carriage in children following heptavalent pneumococcal conjugate vaccination in infancy. *Arch Dis Child*. 2003;88:211–214.
87. Dagan R, Givon-Lavi N, Zamir O, et al. Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. *J Infect Dis*. 2002;185:927–936.
88. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348:1737–1746.
89. McCool TL, Cate TR, Moy G, et al. The immune response to pneumococcal proteins during experimental human carriage. *J Exp Med*. 2002;195:359–365.
90. Malley R, Trzcinski K, Srivastava A, et al. CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. *Proc Natl Acad Sci USA*. 2005;102:4848–4853.
91. Cohen JM, Khandavilli S, Camberlein E, et al. Protective contributions against invasive *Streptococcus pneumoniae* pneumonia of antibody and Th17-cell responses to nasopharyngeal colonisation. *PLoS ONE*. 2011;6:e25558.
92. Olliver M, Hiew J, Mellroth P, et al. Human monocytes promote Th1 and Th17 responses to *Streptococcus pneumoniae*. *Infect Immun*. 2011;79:4210–4217.
93. Musher DM. The gram-positive cocci: I. Streptococci. *Hosp Pract (Off Ed)*. 1988;23:63–76.
94. Musher DM, Chapman AJ, Goree A, et al. Natural and vaccine-related immunity to *Streptococcus pneumoniae*. *J Infect Dis*. 1986;154:245–256.
95. Romero-Steiner S, Libutti D, Pais LB, et al. Standardization of an opsonophagocytic assay for the measurement of functional antibody activity against *Streptococcus pneumoniae* using differentiated HL-60 cells. *Clin Diagn Lab Immunol*. 1997;4:415–422.
96. Rubins JB, Puri AK, Loch J, et al. Magnitude, duration, quality, and function of pneumococcal vaccine responses in elderly adults. *J Infect Dis*. 1998;178:431–440.
97. Musher DM, Johnson B Jr, Watson DA. Quantitative relationship between anticapsular antibody measured by enzyme-linked immunosorbent assay or radioimmunoassay and protection of mice against challenge with *Streptococcus pneumoniae* serotype 4. *Infect Immun*. 1990;58:3871–3876.
98. Janoff EN, Rubins JB. Invasive pneumococcal disease in the immunocompromised host. *Microb Drug Resist*. 1997;3:215–232.
99. Ambrosino DM, Schiffman G, Gotschlich EC, et al. Correlation between G2M(n) immunoglobulin allotype and human antibody response and susceptibility to polysaccharide encapsulated bacteria. *J Clin Invest*. 1985;75:1935–1942.
100. Siber GR, Schur PH, Aisenberg AC, et al. Correlation between serum IgG2 concentrations and the antibody response to bacterial polysaccharide antigens. *N Engl J Med*. 1980;303:178–182.
101. Picard C, Puel A, Bustamante J, et al. Primary immunodeficiencies associated with pneumococcal disease. *Curr Opin Allergy Clin Immunol*. 2003;3:451–459.
102. Cunningham-Rundles C. Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. *J Clin Immunol*. 1989;9:22–33.
103. Umetsu DT, Ambrosino DM, Quinti I, et al. Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG subclass deficiency. *N Engl J Med*. 1985;313:1247–1251.
104. Ambrosino DM, Siber GR, Chilmonczyk BA, et al. An immunodeficiency characterized by impaired antibody responses to polysaccharides. *N Engl J Med*. 1987;316:790–793.
105. Sanders LA, Rijkers GT, Kuis W, et al. Defective antipneumococcal polysaccharide antibody response in children with recurrent respiratory tract infections. *J Allergy Clin Immunol*. 1993;91:110–119.
106. Musher DM, Phan HM, Baughn RE. Protection against bacteremic pneumococcal infection by antibody to pneumolysin. *J Infect Dis*. 2001;183:827–830.
107. Rapola S, Kilpi T, Lahdenkari M, et al. Do antibodies to pneumococcal surface adhesin a prevent pneumococcal involvement in acute otitis media? *J Infect Dis*. 2001;184:577–581.
108. Ojal J, Goldblatt D, Tigoi C, et al. Effect of Maternally Derived Anti-protein and Anticapsular IgG Antibodies on the Rate of Acquisition of Nasopharyngeal Carriage of Pneumococcus in Newborns. *Clin Infect Dis*. 2018;66:121–130.
109. Lipsitch M, Whitney CG, Zell E, et al. Are anticapsular antibodies the primary mechanism of protection against invasive pneumococcal disease? *PLoS Med*. 2005;2:e15.
110. Hostetter MK. Interactions of *Streptococcus pneumoniae* with complement proteins. In: Siber G, Klugman KP, Makela P, eds. *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*. Washington, DC: American Society for Microbiology Press; 2008.
111. Weller S, Reynaud CA, Weill JC. Vaccination against encapsulated bacteria in humans: paradoxes. *Trends Immunol*. 2005;26:85–89.
112. Subramaniam K, Metzger B, Hanau LH, et al. IgM(+) memory B cell expression predicts HIV-associated cryptococcosis status. *J Infect Dis*. 2009;200:244–251.
113. Hart M, Steel A, Clark SA, et al. Loss of discrete memory B cell subsets is associated with impaired immunization responses in HIV-1 infection and may be a risk factor for invasive pneumococcal disease. *J Immunol*. 2007;178:8212–8220.
114. Llupia A, Vilella A, Costas L, et al. Can the response to 23-valent pneumococcal vaccine in splenectomised patients be predicted? *Vaccine*. 2012;30:2382–2386.
115. Carson PJ, Schut RL, Simpson ML, et al. Antibody class and subclass responses to pneumococcal polysaccharides following immunization of human immunodeficiency virus-infected patients. *J Infect Dis*. 1995;172:340–345.
116. Park S, Nahm MH. Older adults have a low capacity to opsonize pneumococci due to low IgM antibody response to pneumococcal vaccinations. *Infect Immun*. 2011;79:314–320.
117. Siber GR. Pneumococcal disease: prospects for a new generation of vaccines. *Science*. 1994;265:1385–1387.
118. Snapper CM. Differential regulation of protein- and polysaccharide-specific Ig isotype production in vivo in response to intact *Streptococcus pneumoniae*. *Curr Protein Pept Sci*. 2006;7:295–305.
119. Avci FY, Li X, Tsuji M, et al. A mechanism for glycoconjugate vaccine activation of the adaptive immune system and its implications for vaccine design. *Nat Med*. 2011;17:1602–1609.
120. Khan AQ, Lees A, Snapper CM. Differential regulation of IgG anti-capsular polysaccharide and antiprotein responses to intact *Streptococcus pneumoniae* in the presence of cognate CD4+ T cell help. *J Immunol*. 2004;172:532–539.
121. Vernacchio L, Romero-Steiner S, Martinez JE, et al. Comparison of an opsonophagocytic assay and IgG ELISA to assess responses to pneumococcal polysaccharide and pneumococcal conjugate vaccines in children and young adults with sickle cell disease. *J Infect Dis*. 2000;181:1162–1166.
122. Styrt B. Infection associated with asplenia: risks, mechanisms, and prevention. *Am J Med*. 1990;88:33N–42N.
123. Wara DW. Host defense against *Streptococcus pneumoniae:* the role of the spleen. *Rev Infect Dis*. 1981;3:299–309.
124. Jandl JH, Jones AR, Castle WB. The destruction of red cells by antibodies in man. I. Observations on the sequestration and lysis of red cells altered by immune mechanisms. *J Clin Invest*. 1957;36:1428–1459.
125. Frank MM, Hosea SW, Brown EJ, et al. Opsonic requirements for intravascular clearance after splenectomy. *N Engl J Med*. 1981;304:245–250.
126. Selby C, Hart S, Ispahani P, et al. Bacteremia in adults after splenectomy or splenic irradiation. *Q J Med*. 1987;63:523–530.
127. Wong WY, Overturf GD, Powars DR. Infection caused by *Streptococcus pneumoniae* in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis, and vaccination. *Clin Infect Dis*. 1992;14:1124–1136.
128. Ballow M, Shira JE, Harden L, et al. Complete absence of the third component of complement in man. *J Clin Invest*. 1975;56:703–710.
129. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev*. 1991;4:359–395.
130. Eisen DP, Dean MM, Boermeester MA, et al. Low serum mannose-binding lectin level increases the risk of death due to pneumococcal infection. *Clin Infect Dis*. 2008;47:510–516.
131. Roy S, Knox K, Segal S, et al. MBL genotype and risk of invasive pneumococcal disease: a case-control study. *Lancet*. 2002;359:1569–1573.
132. Anderson DC, Schmalstieg FC, Finegold MJ, et al. The severe and moderate phenotypes of heritable Mac-1, LFA-1 deficiency: their quantitative definition and relation to leukocyte dysfunction and clinical features. *J Infect Dis*. 1985;152:668–689.
133. Beam TRJ, Allen JC. Patterns of infection in untreated acute leukemia: impact of initial hospitalization. *South Med J*. 1979;72:282–286.
134. Savage DG, Lindenbaum J, Garrett TJ. Biphasic pattern of bacterial infection in multiple myeloma. *Ann Intern Med*. 1982;96:47–50.
135. Yee AMF, Phan HM, Zuniga R, et al. The FcγRIIa-R131 allotype increases risk for bacteremic pneumococcal infections. *Clin Infect Dis*. 1999;30:25–28.
136. Gluckman SJ, Dvorak VC, MacGregor RR. Host defenses during prolonged alcohol consumption in a controlled environment. *Arch Intern Med*. 1977;137:1539–1543.
137. Young CL, MacGregor RR. Alcohol and host defenses: infectious consequences. *Infect Med*. 1989;6:163–175.
138. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. *Medicine (Baltimore)*. 1990;69:307–316.
139. Rahav G, Toledano Y, Engelhard D, et al. Invasive pneumococcal infections. A comparison between adults and children. *Medicine (Baltimore)*. 1997;76:295–303.
140. Watanakunakorn C, Bailey TA. Adult bacteremic pneumococcal pneumonia in a community teaching hospital, 1992-1996. A detailed analysis of 108 cases. *Arch Intern Med*. 1997;157:1965–1971.
141. Mowat AG, Baum J. Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. *N Engl J Med*. 1980;142:869–875.
142. Repine JE, Clawson CC, Goetz FC. Bactericidal function of neutrophils from patients with acute bacterial infections and from diabetics. *J Infect Dis*. 1980;6:869–875.
143. High KP, Akbar AN, Nikolich-Zugich J. Translational research in immune senescence: assessing the relevance of current models. *Semin Immunol*. 2012;24:373–382.
144. Ademokun A, Wu YC, Dunn-Walters D. The ageing B cell population: composition and function. *Biogerontology*. 2010;11:125–137.
145. Frasca D, Diaz A, Romero M, et al. Age effects on B cells and humoral immunity in humans. *Ageing Res Rev*. 2011;10:330–335.
146. Tangye SG, Good KL. Human IgM+CD27+ B cells: memory B cells or "memory" B cells? *J Immunol*. 2007;179:13–19.
147. Weill JC, Weller S, Reynaud CA. Human marginal zone B cells. *Annu Rev Immunol*. 2009;27:267–285.
148. Weller S, Mamani-Matsuda M, Picard C, et al. Somatic diversification in the absence of antigen-driven responses is the hallmark of the IgM+ IgD+ CD27+ B cell repertoire in infants. *J Exp Med*. 2008;205:1331–1342.
149. Shi Y, Yamazaki T, Okubo Y, et al. Regulation of aged humoral immune defense against pneumococcal bacteria by IgM memory B cell. *J Immunol*. 2005;175:3262–3267.
150. Hamza SA, Mousa SM, Taha SE, et al. Immune response of 23-valent pneumococcal polysaccharide vaccinated elderly and its relation to frailty indices, nutritional status, and serum zinc levels. *Geriatr Gerontol Int*. 2012;12:223–229.
151. Ridda I, Macintyre CR, Lindley R, et al. Immunological responses to pneumococcal vaccine in frail older people. *Vaccine*. 2009;27:1628–1636.
152. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in

pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis*. 2008;198:962–970.

153. Hodges R, MacLeod C. Epidemic pneumococcal pneumonia. II. The influence of population characteristics and the environment. *Am J Hyg*. 1946;44:193–206.
154. Fainstein V, Musher DM, Cate TR. Bacterial adherence to pharyngeal cells during viral infection. *J Infect Dis*. 1980;141:172–176.
155. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev*. 2006;19:571–582.
156. Cortese MM, Wolff M, Almeido-Hill J, et al. High incidence rates of invasive pneumococcal disease in the White Mountain Apache population. *Arch Intern Med*. 1992;152:2277–2282.
157. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. *N Engl J Med*. 1995;333:845–851.
158. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of *Pneumocystis carinii* pneumonia, in the United States. *J Infect Dis*. 2001;183:1409–1412.
159. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
160. Redd SC, Rutherford GW, Sande MA, et al. The role of human immunodeficiency virus in pneumococcal bacteremia in San Francisco residents. *J Infect Dis*. 1990;162:1012–1017.
161. Gilks CF, Ojoo SA, Ojoo JC, et al. Invasive pneumococcal disease in a cohort of predominantly HIV-1 infected female sex-workers in Nairobi, Kenya. *Lancet*. 1996;347:718–723.
162. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis*. 2006;43:90–98.
163. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med*. 2000;160:2633–2638.
164. de Gaetano Donati K, Bertagnolio S, Tumbarello M, et al. Effect of highly active antiretroviral therapy on the incidence of bacterial pneumonia in HIV-infected subjects. *Int J Antimicrob Agents*. 2000;16:357–360.
165. Sullivan JH, Moore RD, Keruly JC, et al. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J Respir Crit Care Med*. 2000;162:64–67.
166. Tumbarello M, Tacconelli E, Donati KG, et al. HIV-associated bacteremia: how it has changed in the highly active antiretroviral therapy (HAART) era. *J Acquir Immune Defic Syndr*. 2000;23:145–151.
167. Nuorti JP, Butler JC, Gelling L, et al. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. *Ann Intern Med*. 2000;132:182–190.
168. Paul S, Gilbert HM, Ziecheck W, et al. The impact of potent antiretroviral therapy on the characteristics of hospitalized patients with HIV infection. *AIDS*. 1999;13:415–418.
169. Sansone GR, Frengley JD. Impact of HAART on causes of death of persons with late-stage AIDS. *J Urban Health*. 2000;77:166–175.
170. Benito N, Rano A, Moreno A, et al. Pulmonary infiltrates in HIV-infected patients in the highly active antiretroviral therapy era in Spain. *J Acquir Immune Defic Syndr*. 2001;27:35–43.
171. Ives NJ, Gazzard BG, Easterbrook PJ. The changing pattern of AIDS-defining illnesses with the introduction of highly active antiretroviral therapy (HAART) in a London clinic. *J Infect*. 2001;42:134–139.
172. Obaro SK, Pugatch D, Luzuriaga K. Immunogenicity and efficacy of childhood vaccines in HIV-1-infected children. *Lancet Infect Dis*. 2004;4:510–518.
173. Pancharoen C, Ananworanich J, Thisyakorn U. Immunization for persons infected with human immunodeficiency virus. *Curr HIV Res*. 2004;2:293–299.
174. Rivas P, Herrero MD, Puente S, et al. Immunizations in HIV-infected adults. *AIDS Rev*. 2007;9:173–187.
175. Brunell PA, Vimal V, Sandu M, et al. Abnormalities of measles antibody response in human immunodeficiency virus type 1 (HIV-1) infection. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;10:540–548.
176. Malaspina A, Moir S, Orsega SM, et al. Compromised B cell responses to influenza vaccination in HIV-infected individuals. *J Infect Dis*. 2005;191:1442–1450.
177. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. 2000;355:2106–2111.
178. French N, Gilks CF, Mujugira A, et al. Pneumococcal vaccination in HIV-1-infected adults in Uganda: humoral response and two vaccine failures. *AIDS*. 1998;12:1683–1689.
179. French N, Moore M, Haikala R, et al. A case-control study to investigate serological correlates of clinical failure of 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults. *J Infect Dis*. 2004;190:707–712.
180. Rueda AM, Serpa JA, Matloobi M, et al. The spectrum of invasive pneumococcal disease at an adult tertiary care hospital in the early 21st century. *Medicine (Baltimore)*. 2010;89:331–336.
181. Raz R, Elhanan G, Shimoni Z, et al. Pneumococcal bacteremia in hospitalized Israeli adults: epidemiology and resistance to penicillin. *Clin Infect Dis*. 1997;24:1164–1168.
182. Vergison A, Dagan R, Arguedas A, et al. Otitis media and its consequences: beyond the earache. *Lancet Infect Dis*. 2010;10:195–203.
183. Xu Q, Kaur R, Casey JR, et al. Identification of *Streptococcus pneumoniae* and *Haemophilus influenzae* in culture-negative middle ear fluids from children with acute otitis media by combination of multiplex PCR and multi-locus sequencing typing. *Int J Pediatr Otorhinolaryngol*. 2011;75:239–244.
184. Schwartz LE, Brown RB. Purulent otitis media in adults. *Arch Intern Med*. 1992;152:2301–2304.
185. Gray BM, Dillon HC Jr. Epidemiological studies of *Streptococcus pneumoniae* in infants: antibody to types 3, 6, 14, and 23 in the first two years of life. *J Infect Dis*. 1988;158:948–955.
186. Gwaltney JMJ, Scheld WM, Sande MA, et al. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. *J Allergy Clin Immunol*. 1992;90:457–462.
187. Gwaltney JMJ, Phillips CD, Miller RD, et al. Computed tomographic study of the common cold. *N Engl J Med*. 1994;330:25–30.
188. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012;54:e72–e112.
189. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. *N Engl J Med*. 1992;327:864–872.
190. Saez-Llorens X, McCracken GH Jr. Bacterial meningitis in children. *Lancet*. 2003;361:2139–2148.
191. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med*. 2011;364:2016–2025.
192. Brandt CT, Simonsen H, Liptrot M, et al. In vivo study of experimental pneumococcal meningitis using magnetic resonance imaging. *BMC Med Imaging*. 2008;8:1.
193. Koedel U, Scheld WM, Pfister HW. Pathogenesis and pathophysiology of pneumococcal meningitis. *Lancet Infect Dis*. 2002;2:721–736.
194. Reefhuis J, Honein MA, Whitney CG, et al. Risk of bacterial meningitis in children with cochlear implants. *N Engl J Med*. 2003;349:435–445.
195. Hand WL, Sanford JP. Posttraumatic bacterial meningitis. *Ann Intern Med*. 1970;72:869–874.
196. Eavey RD, Gao Y, Schuknecht HF, et al. Otologic features of bacterial meningtis of childhood. *J Pediatr*. 1985;136:2025–2029.
197. Fillon S, Soulis K, Rajasekaran S, et al. Platelet-activating factor receptor and innate immunity: uptake of gram-positive bacterial cell wall into host cells and cell-specific pathophysiology. *J Immunol*. 2006;177:6182–6191.
198. Klein M, Obermaier B, Angele B, et al. Innate immunity to pneumococcal infection of the central nervous system depends on Toll-like receptor (TLR) 2 and TLR4. *J Infect Dis*. 2008;198:1028–1036.
199. Bhatt SM, Lauretano A, Cabellos C, et al. Progression of hearing loss in experimental pneumococcal meningtis: correlation with cerebrospinal fluid cytochemistry. *J Infect Dis*. 1993;167:675–683.
200. Tuomanen EI, Austrian R, Masure HR. Pathogenesis of pneumococcal infection. *N Engl J Med*. 1995;332:1280–1284.
201. Dunbar SA, Eason RA, Musher DM, et al. Microscopic examination and broth culture of cerebrospinal fluid in diagnosis of meningitis. *J Clin Microbiol*. 1998;36:1617–1620.
202. Perkins MD, Mirrett S, Reller LB. Rapid bacterial antigen detection is not clinically useful. *J Clin Microbiol*. 1995;33:1486–1491.
203. Chodosh S. Acute bacterial exacerbations in bronchitis and asthma. *Am J Med*. 1987;82:154–163.
204. Chodosh S, McCarty J, Farkas S, et al. Randomized, double-blind study of ciprofloxacin and cefuroxime axetil for treatment of acute bacterial exacerbations of chronic bronchitis. The Bronchitis Study Group. *Clin Infect Dis*. 1998;27:722–729.
205. Sethi S, Evans N, Grant BJ, et al. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 2002;347:465–471.
206. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–382.
207. Johansson N, Kalin M, Tiveljung-Lindell A, et al. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis*. 2010;50:202–209.
208. Musher D, Roig I, Charles G, et al. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. *J Infect*. 2013;67:11–18.
209. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. *Pediatrics*. 2008;122:229–237.
210. Garg S, Jain S, Dawood FS, et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection-United States, 2005-2008. *BMC Infect Dis*. 2015;15:369.
211. Brandenburg JA, Marrie TJ, Coley CM, et al. Clinical presentation, processes and outcomes of care for patients with pneumococcal pneumonia. *J Gen Intern Med*. 2000;15:638–646.
212. Porath A, Schlaeffer F, Pick N, et al. Pneumococcal community-acquired pneumonia in 148 hospitalized adult patients. *Eur J Clin Microbiol Infect Dis*. 1997;16:863–870.
213. Metlay JP, Schulz R, Li Y-H, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch Intern Med*. 1997;157:1453–1459.
214. Murphy TF, Fine BC. Bacteremic pneumococcal pneumonia in the elderly. *Am J Med Sci*. 1984;288:114–118.
215. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA*. 1997;278:1440–1445.
216. Speets AM, Hoes AW, van der Graaf Y, et al. Chest radiography and pneumonia in primary care: diagnostic yield and consequences for patient management. *Eur Respir J*. 2006;28:933–938.
217. Ort S, Ryan RL, Barden G, et al. Pneumococcal pneumonia in hospitalized patients. *JAMA*. 1983;249:214–218.
218. Pande A, Nasir S, Rueda AM, et al. The incidence of necrotizing changes in adults with pneumococcal pneumonia. *Clin Infect Dis*. 2012;54:10–16.
219. Yangco BG, Deresinski SC. Necrotizing or cavitating pneumonia due to *Streptococcus pneumoniae*: report of four cases and review of the literature. *Medicine (Baltimore)*. 1980;59:449–457.
220. Light RW, Girard WM, Jenkinson SG, et al. Parapneumonic effusions. *Am J Med*. 1980;69:507–512.
221. Gardner JG, Bhamidipati DR, Rueda AM, et al. White blood cell counts, alcoholism, and cirrhosis in pneumococcal pneumonia. *Open Forum Infect Dis*. 2017;4:ofx034.
222. Musher DM, Rueda AM, Kaka AS, et al. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis*. 2007;45:158–165.
223. Perlino CA. Laboratory diagnosis of pneumonia due to *Streptococcus pneumoniae*. *J Infect Dis*. 1984;150:139–144.
224. 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;44(suppl 2):S27–S72.
225. Deleted in review.
226. Dowell SF, Garman RL, Liu G, et al. Evaluation of Binax NOW, an assay for the detection of pneumococcal antigen in urine samples, performed among pediatric patients. *Clin Infect Dis*. 2001;32:824–825.
227. Song JY, Eun BW, Nahm MH. Diagnosis of pneumococcal pneumonia: current pitfalls and the way forward. *Infect Chemother*. 2013;45:351–366.
228. Pontoizeau C, Dangers L, Jarlier V, et al. Ruling out false-positive urinary *Legionella pneumophilia* serogroup 1 and *Streptococcus pneumoniae* antigen test results by heating urine. *J Clin Microbiol*. 2014;52:4347–4349.
229. Wunderink RG, Self WH, Anderson EJ, et al. Pneumococcal community-acquired pneumonia detected

by serotype-specific urinary antigen detection assays. *Clin Infect Dis*. 2018;66:1504–1510.
230. Albrich WC, Madhi SA, Adrian PV, et al. Pneumococcal colonisation density: a new marker for disease severity in HIV-infected adults with pneumonia. *BMJ Open*. 2014;4:e005953.
231. Stralin K, et al. Comparison of sputum and nasopharyngeal aspirate samples and of the PCR gene targets *lytA* and *Spn9802* for quantitative PCR for rapid detection of pneumococcal pneumonia. *J Clin Microbiol*. 2014;52:83–89.
232. Gadsby NJ, et al. Development of two real-time multiplex PCR assays for the detection and quantification of eight key bacterial pathogens in lower respiratory tract infections. *Clin Microbiol Infect*. 2015;21:788.e1–788.e13.
233. Messaoudi M, Milenkov M, Albrich WC, et al. The Relevance of a Novel Quantitative Assay to Detect up to 40 Major *Streptococcus pneumoniae* Serotypes Directly in Clinical Nasopharyngeal and Blood Specimens. *PLoS ONE*. 2016;11:e0151428.
234. Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. *Clin Infect Dis*. 2016;62:817–823.
235. Anstadt MP, Guill CK, Gordon HS, et al. Surgical vs. nonsurgical treatment of empyema: an outcomes analysis. *Am J Med Sci*. 2003;326:9–14.
236. Powderly WG, Stanley SL Jr, Medoff G. Pneumococcal endocarditis: report of a series and review of the literature. *Rev Infect Dis*. 1986;8:786–791.
237. Lindberg J, Prag J, Schonheyder HC. Pneumococcal endocarditis is not just a disease of the past: an analysis of 16 cases diagnosed in Denmark 1986-1997. *Scand J Infect Dis*. 1998;30:469–472.
238. Lefort A, Mainardi JL, Selton-Suty C, et al. *Streptococcus pneumoniae* endocarditis in adults. A multicenter study in France in the era of penicillin resistance (1991-1998). The Pneumococcal Endocarditis Study Group. *Medicine (Baltimore)*. 2000;79:327–337.
239. Case Records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 49-1990. A 47-year-old Cape Verdean man with pericardial disease. *N Engl J Med*. 1990;323:1614–1624.
240. Dugi DD 3rd, Musher DM, Clarridge JE 3rd, et al. Intraabdominal infection due to *Streptococcus pneumoniae*. *Medicine (Baltimore)*. 2001;80:236–244.
241. Rahav G, Ben-David L, Persitz E. Postmenopausal pneumococcal tubo-ovarian abscess. *Rev Infect Dis*. 1991;13:896–897.
242. Robinson ENJ. Pneumococcal endometritis and neonatal sepsis. *Rev Infect Dis*. 1990;12:416–422.
243. Westh H, Skibsted L, Korner B. *Streptococcus pneumoniae* infections of the female genital tract and in the newborn child. *Rev Infect Dis*. 1990;12:416–422.
244. Ryczak M, Sands M, Brown RB, et al. Pneumococcal arthritis in a prosthetic knee. A case report and review of the literature. *Clin Orthop*. 1987;224–227.
245. Morley PK, Hull RG, Hall MA. Pneumococcal septic arthritis in rheumatoid arthritis. *Ann Rheum Dis*. 1987;46:482–484.
246. Raad J, Peacock JE Jr. Septic arthritis in the adult caused by *Streptococcus pneumoniae*: a report of 4 cases and review of the literature. *Semin Arthritis Rheum*. 2004;34:559–569.
247. Turner DP, Weston VC, Ispahani P. *Streptococcus pneumoniae* spinal infection in Nottingham, United Kingdom: not a rare event. *Clin Infect Dis*. 1999;28:873–881.
248. Grigoriadis E, Gold WL. Pyogenic brain abscess caused by *Streptococcus pneumoniae:* case report and review. *Clin Infect Dis*. 1997;25:1108–1112.
249. DiNubile MJ, Albornoz MA, Stumacher RJ, et al. Pneumococcal soft-tissue infections: possible association with connective tissue diseases. *J Infect Dis*. 1991;163:897–900.
250. Peters NS, Eykyn SJ, Rudd AG. Pneumococcal cellulitis: a rare manifestation of pneumococcaemia in adults. *J Infect*. 1989;19:57–59.
251. Capdevila O, Grau I, Vadillo M, et al. Bacteremic pneumococcal cellulitis compared with bacteremic cellulitis caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. *Eur J Clin Microbiol Infect Dis*. 2003;22:337–341.
252. Rodriguez Barradas MC, Musher DM, Hamill RJ, et al. Unusual manifestations of pneumococcal infection in human immunodeficiency virus-infected individuals: the past revisited. *Clin Infect Dis*. 1992;14:192–199.
253. Hibbs JR, Douglas JM Jr, Judson FN, et al. Prevalence of human immunodeficiency virus infection, mortality rate, and serogroup distribution among patients with pneumococcal bacteremia at Denver General Hospital, 1984-1994. *Clin Infect Dis*. 1997;25:195–199.
254. Smeeth L, Casas JP, Hingorani AD. The role of infection in cardiovascular disease: more support but many questions remain. *Eur Heart J*. 2007;28:1178–1179.
255. Smeeth L, Thomas SL, Hall AJ, et al. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351:2611–2618.
256. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis*. 2010;10:83–92.
257. Brown AO, Mann B, Gao G, et al. *Streptococcus pneumoniae* translocates into the myocardium and forms unique microlesions that disrupt cardiac function. *PLoS Pathog*. 2014;10:e1004383.
258. Spinale JM, Ruebner RL, Kaplan BS, et al. Update on *Streptococcus pneumoniae* associated hemolytic uremic syndrome. *Curr Opin Pediatr*. 2013;25:203–208.
259. Appelbaum PC. Antimicrobial resistance in *Streptococcus pneumoniae:* an overview. *Clin Infect Dis*. 1992;15.
260. Musher DM, Bartlett JG, Doern GV. A fresh look at the definition of susceptibility of *Streptococcus pneumoniae* to beta-lactam antibiotics. *Arch Intern Med*. 2001;161:2538–2544.
261. Hieber JP, Nelson JD. A pharmacologic evaluation of penicillin in children with purulent meningitis. *N Engl J Med*. 1977;297:410–413.
262. Centers for Disease Control and Prevention. Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*—United States, 2006-2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:1353–1355.
263. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus *Streptococcus pneumoniae:* coping with antimicrobial susceptibility in an era of resistance. *Clin Infect Dis*. 2009;48:1596–1600.
264. Smith AM, Klugman KP. Alterations in penicillin-binding protein 2B from penicillin-resistant wild-type strains of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 1995;859–867.
265. Smith AM, Klugman KP, Coffey TJ, et al. Genetic diversity of penicillin-binding protein 2B and 2X genes from *Streptococcus pneumoniae* in South Africa. *Antimicrob Agents Chemother*. 1993;37:1938–1944.
266. McDougal LK, Rasheed JK, Biddle JW, et al. Identification of multiple clones of extended-spectrum cephalosporin-resistant *Streptococcus pneumoniae* isolates in the United States. *Antimicrob Agents Chemother*. 1995;39:2282–2288.
267. Dowson CG, Coffey TJ, Kell C, et al. Evolution of penicillin resistance in *Streptococcus pneumoniae;* the role of *Streptococcus mitis* in the formation of a low affinity PBP2B in S. pneumoniae. *Mol Microbiol*. 1993;9:635–643.
268. Versalovic J, Kapur V, Mason EO Jr, et al. Penicillin-resistant *Streptococcus pneumoniae* strains recovered in Houston: identification and molecular characterization of multiple clones. *J Infect Dis*. 1993;167:850–856.
269. Tomasz A. Antibiotic resistance in *Streptococcus pneumoniae*. *Clin Infect Dis*. 1997;24(suppl 1):S85–S88.
270. Soares S, Kristinsson KG, Musser JM, et al. Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late l980s. *J Infect Dis*. 1993;168:158–163.
271. Richter SS, Heilmann KP, Coffman SL, et al. The molecular epidemiology of penicillin-resistant *Streptococcus pneumoniae* in the United States, 1994-2000. *Clin Infect Dis*. 2002;34:330–339.
272. Hurmic O, Grall N, Al Nakib M, et al. Evidence of a clonal expansion of *Streptococcus pneumoniae* serotype 19A in adults as in children assessed by the DiversiLab(R) system. *Eur J Clin Microbiol Infect Dis*. 2014;33:2067–2073.
273. Musher DM Resistance of *Streptococcus pneumoniae* to the Macrolides, Lincosamines, and Ketolides. http://www.uptodate.com/contents/resistance-of-streptococcus-pneumoniae-to-the-macrolides-azalides-lincosamines-and-ketolides. Accessed March 25, 2014.
274. Musher DM, Dowell ME, Shortridge VD, et al. Emergence of macrolide resistance during treatment of pneumococcal pneumonia. *N Engl J Med*. 2002;346:630–631.
275. Musher DM. Resistance of *Streptococcus pneumoniae* to beta-lactam antibiotics. In: Sexton DJ, ed. *UpToDate: Infectious Diseases*. Waltham, MA: UpToDate; 2018.
276. Sahm DF, Brown NP, Draghi DC, et al. Tracking resistance among bacterial respiratory tract pathogens: summary of findings of the TRUST Surveillance Initiative, 2001-2005. *Postgrad Med*. 2008;120:8–15.
277. Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N Engl J Med*. 2009;360:244–256.
278. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: a sociocultural perspective. *Emerg Infect Dis*. 2002;8:1460–1467.
279. Jenkins SG, Farrell DJ. Increase in pneumococcus macrolide resistance, United States. *Emerg Infect Dis*. 2009;15:1260–1264.
280. Chen DK, McGeer A, de Azavedo JC, et al. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *N Engl J Med*. 1999;341:233–239.
281. Weiss K, Restieri C, Gauthier R, et al. A nosocomial outbreak of fluoroquinolone-resistant *Streptococcus pneumoniae*. *Clin Infect Dis*. 2001;33:517–522.
282. Kupronis BA, Richards C, Whitney CG. Invasive pneumococcal disease among the elderly residing in long-term care facilities and community-living elderly. *J Am Geriatr Soc*. 2003;51:1520–1525.
283. Ben-David D, Schwaber MJ, Adler A, et al. Persistence and complex evolution of fluoroquinolone-resistant *Streptococcus pneumoniae* clone. *Emerg Infect Dis*. 2014;20:799–805.
284. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964.
285. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130:1–45.
286. Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. *Clin Infect Dis*. 2002;35:556–564.
287. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.
288. Capelastegui A, Espana PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Respir J*. 2006;27:151–157.
289. Garin N, Genne D, Carballo S, et al. Beta-Lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med*. 2014;174:1894–1901.
290. Nie W, Li B, Xiu Q. Beta-Lactam/macrolide dual therapy versus beta-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69:1441–1446.
291. Horita N, Otsuka T, Haranaga S, et al. Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: a systematic review and meta-analysis. *Respirology*. 2016;21:1193–1200.
292. Corrales-Medina VF, Musher DM. Immunomodulatory agents in the treatment of community-acquired pneumonia: a systematic review. *J Infect*. 2011;63:187–199.
293. Musher DM Resistance of *Streptococcus pneumoniae* to Beta-Lactam Antibiotics. http://www.uptodate.com/contents/resistance-of-streptococcus-pneumoniae-to-beta-lactam-antibiotics. Accessed March 25, 2014.
294. File TMJ, Tan JS. Optimizing therapy for community-acquired pneumonia with the goal of rapid resolution of illness. *Clin Infect Dis*. 2005;41:1706–1708.
295. Bordon J, Peyrani P, Brock GN, et al. The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. *Chest*. 2008;133:618–624.
296. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347:1549–1556.
297. Brouwer MC, McIntyre P, de Gans J, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2010;(9):CD004405.
298. Omer SB, Zaman K, Roy E, et al. Combined effects of antenatal receipt of influenza vaccine by mothers and pneumococcal conjugate vaccine receipt by infants: results from a randomized, blinded, controlled trial. *J Infect Dis*. 2013;207:1144–1147.
299. Centers for Disease Control and Prevention. Invasive pneumococcal disease and 13-valent pneumococcal conjugate vaccine (PCV13) coverage among children aged ≤59 months—selected U.S. regions, 2010-2011. *MMWR Morb Mortal Wkly Rep*. 2011;60:1477–1481.
300. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J*. 2000;19:187–195.
301. Bliss SJ, O'Brien KL, Janoff EN, et al. The evidence for using conjugate vaccines to protect HIV-infected children against pneumococcal disease. *Lancet Infect Dis*. 2008;8:67–80.
302. Musher DM, Groover JE, Rowland JM, et al. Antibody to capsular polysaccharides of Streptococcus pneumoniae: prevalence, persistence, and response to revaccination. *Clin Infect Dis*. 1993;17:66–73.

303. Musher DM, Luchi MJ, Watson DA, et al. Pneumococcal polysaccharide vaccine in young adults and older bronchitics: determination of IgG responses by ELISA and the effect of adsorption of serum with non-type-specific cell wall polysaccharide. *J Infect Dis*. 1990;161:728–735.
304. Johnson S, Opstad NL, Douglas JM Jr, et al. Prolonged and preferential production of polymeric immunoglobulin A in response to *Streptococcus pneumoniae* capsular polysaccharides. *Infect Immun*. 1996;64:4339–4344.
305. Torling J, Hedlund J, Konradsen HB, et al. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. *Vaccine*. 2003;22:96–103.
306. Romero-Steiner S, Musher DM, Cetron MS, et al. Reduction in functional antibody activity against *Streptococcus pneumoniae* in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. *Clin Infect Dis*. 1999;29:281–288.
307. Baxendale HE, Davis Z, White HN, et al. Immunogenetic analysis of the immune response to pneumococcal polysaccharide. *Eur J Immunol*. 2000;30:1214–1223.
308. Kolibab K, Smithson SL, Rabquer B, et al. Immune response to pneumococcal polysaccharides 4 and 14 in elderly and young adults: analysis of the variable heavy chain repertoire. *Infect Immun*. 2005;73:7465–7476.
309. O'Brien KL, Hochman M, Goldblatt D. Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness an issue? *Lancet Infect Dis*. 2007;7:597–606.
310. Manoff SB, Liss C, Caulfield MJ, et al. Revaccination with a 23-valent pneumococcal polysaccharide vaccine induces elevated and persistent functional antibody responses in adults aged 65 > or = years. *J Infect Dis*. 2010;201:525–533.
311. de Roux A, Schmoele-Thoma B, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. *Clin Infect Dis*. 2008;46:1015–1023.
312. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis*. 2010;201:32–41.
313. Riley ID, Lehmann D, Alpers MP, et al. Pneumococcal vaccine prevents death from acute lower-respiratory-tract infections in Papua New Guinean children. *Lancet*. 1986;2:877–881.
314. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005;365:1139–1146.
315. Klugman KP, Madhi SA, Huebner RE, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med*. 2003;349:1341–1348.
316. O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. *Lancet*. 2003;362:355–361.
317. Black S, Shinefield H. Safety and efficacy of the seven-valent pneumococcal conjugate vaccine: evidence from Northern California. *Eur J Pediatr*. 2002;161(suppl 2):S127–S131.
318. Madhi SA, Adrian P, Kuwanda L, et al. Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. *Vaccine*. 2007;25:2451–2457.
319. Myint TT, Madhava H, Balmer P, et al. The impact of 7-valent pneumococcal conjugate vaccine on invasive pneumococcal disease: a literature review. *Adv Ther*. 2013;30:127–151.
320. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001;344:403–409.
321. Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J*. 2002;21:810–815.
322. Madhi SA, Kuwanda L, Cutland C, et al. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. *Clin Infect Dis*. 2005;40:1511–1518.
323. Feikin DR, Feldman C, Schuchat A, et al. Global strategies to prevent bacterial pneumonia in adults with HIV disease. *Lancet Infect Dis*. 2004;4:445–455.
324. Griffin MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*. 2013;369:155–163.
325. Olarte L, Barson WJ, Barson RM, et al. Pneumococcal pneumonia requiring hospitalization in US children in the 13-valent pneumococcal conjugate vaccine era. *Clin Infect Dis*. 2017;64:1699–1704.
326. Austrian R, Douglas RM, Schiffman G, et al. Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Physicians*. 1976;89:184–194.
327. Smit P, Oberholzer D, Hayden-Smith K, et al. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA*. 1977;238:2613–2616.
328. Black CL, Williams WW, Warnock R, et al. Pneumococcal vaccination among Medicare beneficiaries occurring after the Advisory Committee on Immunization Practices recommendation for routine use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults aged >/=65 years. *MMWR Morb Mortal Wkly Rep*. 2017;66:728–733.
329. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med*. 1991;325:1453–1460.
330. Farr BM, Johnston L, Cobb DK, et al. Preventing pneumococcal bacteremia in patients at risk. *Arch Intern Med*. 1995;155:2336–2340.
331. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med*. 2003;348:1747–1755.
332. Dominguez A, Salleras L, Fedson DS, et al. Effectiveness of pneumococcal vaccination for elderly people in Catalonia, Spain: a case-control study. *Clin Infect Dis*. 2005;40:1250–1257.
333. Moberley SA, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev*. 2013;(1):CD000422.
334. Huss A, Scott P, Stuck AE, et al. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ*. 2009;180:48–58.
335. Moberley SA, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev*. 2008;(1):CD000422.
336. Austrian R. *Surveillance of Pneumococcal Infection for Field Trials of Polyvalent Pneumococcal Vaccines. Report DAB-VDP-12-84*. Bethesda, MD: National Institutes of Health; 1980:1–84.
337. Koivula I, Sten M, Leinonen M, et al. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. *Am J Med*. 1997;103:281–290.
338. Ortqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. *Lancet*. 1998;351:399–403.
339. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;315:1318–1327.
340. Honkanen PO, Keistinen T, Miettinen L, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. *Vaccine*. 1999;17:2493–2500.
341. Maruyama T, Taguchi O, Niederman MS, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. *BMJ*. 2010;340:c1004.
342. Vila-Corcoles A, Ochoa-Gondar O, Hospital I, et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. *Clin Infect Dis*. 2006;43:860–868.
343. Gaillat J, Zmirou D, Mallaret MR, et al. Clinical trial of an antipneumococcal vaccine in elderly subjects living in institutions. *Rev Epidemiol Sante Publique*. 1985;33:437–444, [in French].
344. Lexau CA, Lynfield R, Danila R, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA*. 2005;294:2043–2051.
345. Centers for Disease Control and Prevention. Licensure of 13-valent pneumococcal conjugate vaccine for adults aged 50 years and older. *MMWR Morb Mortal Wkly Rep*. 2012;61:394–395.
346. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis*. 2015;15:301–309.
347. Feikin DR, Jagero G, Aura B, et al. High rate of pneumococcal bacteremia in a prospective cohort of older children and adults in an area of high HIV prevalence in rural western Kenya. *BMC Infect Dis*. 2010;10:186.
348. Obaro SK, Madhi SA. Bacterial pneumonia vaccines and childhood pneumonia: are we winning, refining, or redefining? *Lancet Infect Dis*. 2006;6:150–161.
349. Ahmed F, Steinhoff MC, Rodriguez-Barradas MC, et al. Effect of human immunodeficiency virus type 1 infection on the antibody response to a glycoprotein conjugate pneumococcal vaccine: results from a randomized trial. *J Infect Dis*. 1996;173:83–90.
350. Musher DM, Ceasar H, Kojic EM, et al. Administration of protein-conjugate pneumococcal vaccine to patients who have invasive disease after splenectomy despite their having received 23-valent pneumococcal polysaccharide vaccine. *J Infect Dis*. 2005;191:1063–1067.
351. Musher DM, Sampath R, Rodriguez-Barradas MC. The potential role for protein-conjugate pneumococcal vaccine in adults: what is the supporting evidence? *Clin Infect Dis*. 2011;52:633–640.
352. Feikin DR, Elie CM, Goetz MB, et al. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. *Vaccine*. 2001;20:545–553.
353. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med*. 2010;362:812–822.
354. Janoff EN, Breiman RF, Daley CL, et al. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med*. 1992;117:314–324.
355. Crum-Cianflone NF, Huppler Hullsiek K, Roediger M, et al. A randomized clinical trial comparing revaccination with pneumococcal conjugate vaccine to polysaccharide vaccine among HIV-infected adults. *J Infect Dis*. 2010;202:1114–1125.
356. Crum-Cianflone NF, Roediger M, Huppler Hullsiek K, et al. The association of ethnicity with antibody responses to pneumococcal vaccination among adults with HIV infection. *Vaccine*. 2010;28:7583–7588.
357. Tasker SA, Wallace MR, Rubins JB, et al. Reimmunization with 23-valent pneumococcal vaccine for patients infected with human immunodeficiency virus type 1: clinical, immunologic, and virologic responses. *Clin Infect Dis*. 2002;34:813–821.
358. Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of the 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:1–19.
359. Tomczyk S, Bennett NM, Stoecker C, et al. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63:822–825.
360. Kobayashi M, Bennett NM, Gierke R, et al. Intervals between PCV13 and PPSV23 vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2015;64:944–947.
361. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
362. Tilghman RC, Finland M. Clinical significance of bacteremia in pneumococcal pneumonia. *Arch Intern Med*. 1937;59:602–619.
363. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution and the isolation of respiratory viruses. *Clin Infect Dis*. 1996;22:100–106.
364. The Joint Commission. Specifications Manual for National Hospital Quality Measures – Pneumococcal Immunization 2015. http://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx.
365. Pneumovax® [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2014.
366. Prevnar® [package insert]. Philadelphia, PA: Pfizer Pharmaceuticals, Inc.; 2015.

200 *Enterococcus* Species, *Streptococcus gallolyticus* Group, and *Leuconostoc* Species

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SHORT VIEW SUMMARY

Microbiology and Taxonomy

- Enterococci are gram-positive facultatively anaerobic bacteria that usually appear oval in shape and can be seen as single cells, pairs, short chains, or very long chains.
- Enterococci are capable of growing in media containing 6.5% sodium chloride and at temperatures between 10°C and 45°C and are able to hydrolyze esculin in the presence of 40% bile salts.
- *Enterococcus faecalis* and *Enterococcus faecium* are the most clinically relevant species.
- The former *Streptococcus bovis* group is now divided into three main species: *S. gallolyticus*, *S. pasteurianus,* and *S. infantarius*.
- The *Leuconostoc* genus comprises catalase-negative, gram-positive cocci that are usually arranged in pairs or chains and are intrinsically resistant to vancomycin.

Colonization, Virulence, and Genomics

- Enterococci are normal commensals of the gastrointestinal tract.
- Enterococci are capable of dominating the gut microbiota of hospitalized patients who receive broad-spectrum antibiotics.
- Specific hospital-associated genetic lineages of *E. faecium* and *E. faecalis* have evolved to become successful in the nosocomial environment.
- The *S. gallolyticus* group of organisms carries genes encoding potential cell surface determinants that interact with host proteins, which may help explain the association with endocarditis and colonic malignancy.

Epidemiology

- Enterococci are known to cause hospital-associated infections, particularly in critically ill or immunosuppressed patients.
- Enterococci are among the most common organisms causing both hospital-associated and community-associated infective endocarditis (IE).
- Enterococci are able to spread in the hospital via the hands of health care workers and via the environment.
- Infection control measures are critical to prevent acquisition of these microorganisms.
- IE and bacteremia caused by *S. gallolyticus* are highly associated with gastrointestinal malignancies.

Clinical Presentations

- Enterococci are capable of causing bloodstream infections in community-associated and hospital-associated clinical settings.
- IE is one of the most serious and life-threatening infections caused by enterococci.
- Enterococci are one of the leading causes of nosocomial urinary tract infections.
- Enterococci have been described in soft tissue infections, intraabdominal infections, and meningitis.
- The *S. gallolyticus* group of organisms can cause bacteremia and IE.
- *Leuconostoc* causes opportunistic infections mainly in immunocompromised patients, although cases in immunocompetent patients have been reported.

Therapy and Antimicrobial Resistance

- Although most *E. faecalis* isolates are susceptible to ampicillin and vancomycin, *E. faecium* isolates typically exhibit high minimal inhibitory concentrations of ampicillin, and most clinical isolates in the United States are vancomycin-resistant.
- Bactericidal therapy for *E. faecalis* often requires the use of a cell wall agent plus an aminoglycoside or ceftriaxone.
- The therapy of choice for severe infections caused by *E. faecalis* is the combination of ampicillin plus either an aminoglycoside (gentamicin or streptomycin) or ceftriaxone.
- Ampicillin plus ceftriaxone is considered an equivalent alternative to ampicillin plus an aminoglycoside as therapy for *E. faecalis* endocarditis.
- Therapy of severe infections caused by vancomycin-resistant *E. faecium* is challenging, and no consistently reliable therapy has been established.
- Linezolid is the only US Food and Drug Administration–approved drug for multidrug-resistant *E. faecium,* but this compound has important limitations because of the lack of bactericidal effect, toxicity, side effects, and emergence of resistance.
- Daptomycin is a lipopeptide antibiotic with in vitro bactericidal activity against enterococci, but development of resistance during therapy seems to be a limitation for the use of this antibiotic.
- Daptomycin combinations (e.g., with β-lactams, aminoglycosides, tigecycline) may offer some promise in the future for treatment of multidrug-resistant enterococcal infections.
- The therapy of choice for endocarditis caused by the *S. gallolyticus* group of organisms is typically a β-lactam, but therapy varies according to the penicillin minimal inhibitory concentration of the organism.
- Ampicillin or penicillin is the drug of choice for treatment of *Leuconostoc* infections.

HISTORICAL BACKGROUND

The first time that the term *entérocoque* was used appears to have been in an article in the French literature in 1899.[1] The article was referring to a diplococcus found in the gastrointestinal (GI) tract that had the potential to become pathogenic for humans. The first clinical and pathologic description of an enterococcal infection was published the same year (1899)[2] and concerned a patient admitted to "Dr. Osler's Service" with a clinical picture of endocarditis who succumbed to the infection. The authors isolated gram-positive cocci in "pairs and short chains" from the patient's blood and several organs (postmortem). The virulence properties of the organism were confirmed after inoculating it into several animal models and reproducing the pathologic findings observed in the patient. This organism was initially designated *Micrococcus zymogenes* because of its fermentative properties. In 1906 Andrews and Horder[3] described in detail a study of streptococci pathogenic for humans and used the name *Streptococcus faecalis* for the first time to denote the most common species of streptococci present in the intestine of humans and other vertebrates. They referred to previous environmental experiments performed by themselves and Houston in London,[3] indicating that the most common microorganisms collected from London's

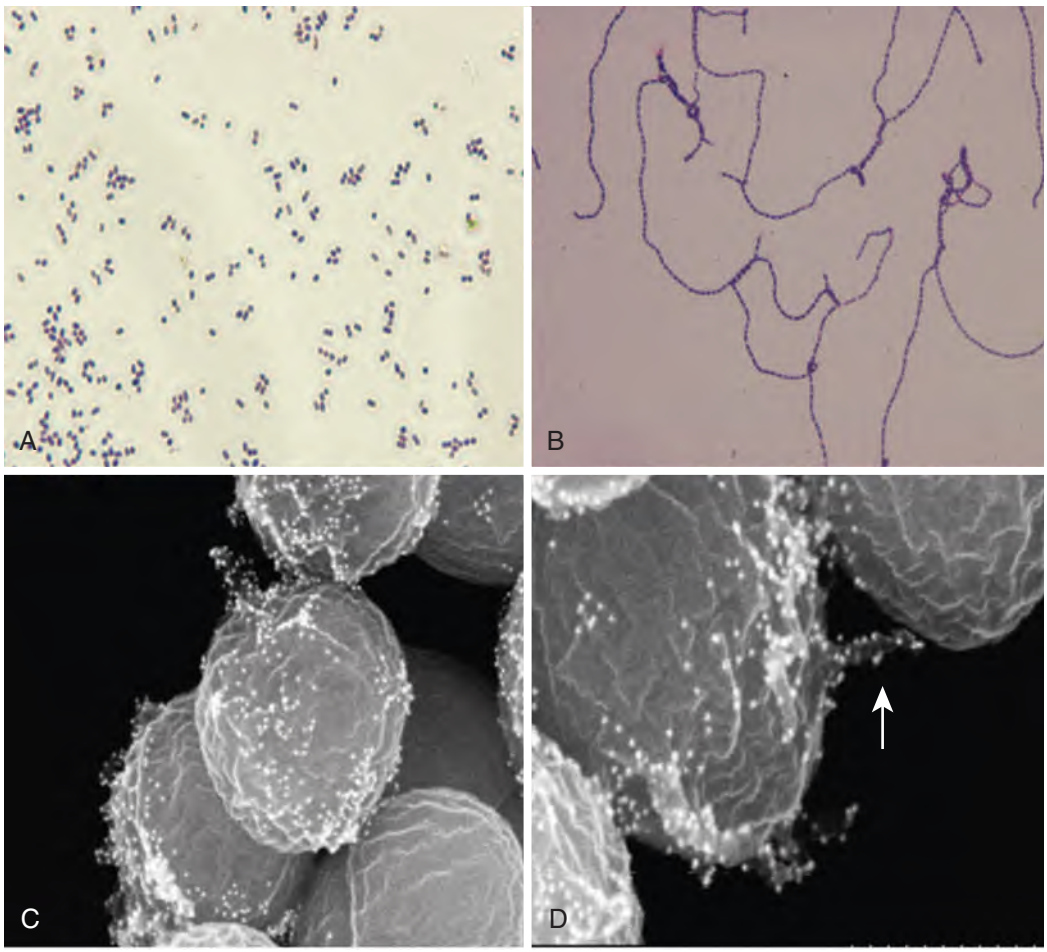

FIG. 200.1 Gram stain and scanning electron microscopy (SEM) of *enterococcus faecalis* isolates. (A) Gram stain of *E. faecalis* V583 after growth in brain heart infusion broth for 5 hours, exhibiting pairs, single cells, and short chains (×100 magnification). (B) *E. faecalis* TX0623, an isolate that produces β-lactamase, showing very long chains after growth using the same conditions indicated in (A) (×50 magnification). (C–D) Immunogold labeling and SEM of *E. faecalis* pili stained with anti-Ebp antibodies (one of the pilus proteins). Pili are seen as projections from the cell surface (*arrow* in D) (C, ×90,000; D, ×150,000 magnification).

air were "intestinal streptococci," which probably originated from horse dung, "which forms so large of a part of the organic contamination of London's air."

In December 1937 Sherman,[4] addressing the Society of American Bacteriologists, indicated that "the enterococcus" was a nonspecific term used for streptococci isolated from the gut, which was "a screen behind which the investigator could hide his ignorance of the organisms with which he worked." Sherman[4] proposed to group the enterococci as *S. faecalis, S. faecalis* var. *hemolyticus, S. faecalis* var. *zymogenes, S. faecalis* var. *liquefaciens,* and *S. durans,* all of which displayed common phenotypic characteristics that included growth in the presence of 6.5% sodium chloride, pH 9.6, and high temperature. Studies in the 1940s and 1950s showed that an organism initially identified in 1919 as *S. faecium*[5] had distinct characteristics that differentiated it from *S. faecalis,*[6,7] and in 1970 a formal proposal that the enterococcal streptococci be considered a new genus based on their distinct phenotypic characteristics was put forward.[8] However, it was not until 1984 that *Enterococcus* was widely confirmed as a separate genus from *Streptococcus* after nucleic acid hybridization experiments were performed, and genetic tools were subsequently applied to differentiate the varied species of enterococci.[9] More recently, using next-generation sequencing technology and molecular clocks to analyze the genomes of an array of representatives of the genus, the emergence of the ancestors of the modern enterococci was estimated to coincide with the advent of terrestrial land animals some 400 million years ago, speaking to the long and successful history of this durable commensal and opportunistic pathogen.[10]

MICROBIOLOGY AND TAXONOMY

Organisms belonging to the genus *Enterococcus* are gram-positive facultatively anaerobic bacteria that usually appear oval in shape and can be seen as single cells, pairs, short chains, or very long chains (Fig. 200.1). They are capable of growing in media containing 6.5% sodium chloride and at temperatures between 10°C and 45°C, and they are able to hydrolyze esculin in the presence of 40% bile salts and produce a leucine aminopeptidase and pyrrolidonyl arylamidase (PYR) (except for *E. cecorum, E. columbae, E. pallens,* and *E. saccharolyticus*). Enterococci are usually α-hemolytic or γ-hemolytic on trypticase soy, 5% sheep blood agar (Table 200.1), whereas some are β-hemolytic (due to the acquisition of a hemolysis/cytolysin gene) on horse, rabbit, or human blood. Most enterococci react with Lancefield group D antisera and some react with group Q antisera, and some of them are motile (e.g., *E. casseliflavus* and *E. gallinarum*). Table 200.2 lists some enterococci spp. isolated from human infections; the vast majority of clinical infections are produced by two species (*E. faecalis* and *E. faecium*), and clinical laboratories usually do not identify enterococci to the species level. However, in certain clinical scenarios or in epidemiologic studies, it may be important to differentiate between these two species because they appear to differ in their virulence and antibiotic resistance profiles (see later).

Conventional methods to identify enterococci at the species level include manual biochemical differentiation based on several tests (e.g., acid formation and hydrolysis of arginine); nonetheless, because of the laboriousness of this approach, laboratories usually rely on automated

TABLE 200.1 Phenotypic Differentiation Among Enterococci, *Leuconostoc,* and *Streptococcus Gallolyticus* Group

	PHENOTYPIC CHARACTERISTICS									
GENUS	**VAN**	**Gas**	**BE**	**PYR**	**LAP**	**NaCl**	**10° C**	**45° C**	**HEM**	**Lancefield Group**
Enterococcus spp.	S/R	—	++	++	++	++	++	++	α/γ	D (+)
Leuconostoc spp.	R	++	+	—	—	+	+/–	+/–	α/γ	D(+/–)
Streptococcus gallolyticus group[a]	S[b]	—	++	—	++	—	+/–	++	α/γ	D (+)

[a]Includes *Streptococcus gallolyticus* subsp. *gallolyticus (S. gallolyticus), S. gallolyticus* subsp. *pasteurianus (S. pasteurianus),* and *S. infantarius* subsp. *infantarium (S. infantarium).*
[b]Vancomycin-resistant isolates carrying the vanB gene cluster have been described.
++, Positive in ≥85% of isolates; *+,* positive in 50%–84% of isolates; *+/–,* positive in 16%–49% of isolates; *—,* positive in ≤15% of isolates; *10°C,* growth at 10°C; *45°C,* growth at 45°C; *BE,* hydrolysis of esculin in the presence of bile; *Gas,* production of gas in de Man, Rogosa, and Sharpe broth; *HEM,* hemolysis in sheep blood agar; *LAP,* production of leucine aminopeptidase; *NaCl,* growth in medium containing 6.5% sodium chloride; *PYR,* production of pyrrolidonyl arylamidase; *R,* resistant; *S,* susceptible; *VAN,* vancomycin susceptibility.
Modified from Teixeira LM, Carvalho MGS, Facklam RR, et al. Enterococcus. In: Murray PR, Baron EJ, Jorgen JH, et al, eds. Manual of Clinical Microbiology. *11th ed. Washington, DC: American Society for Microbiology Press; 2015:403–421.*

TABLE 200.2 Enterococcal Species Isolated From Human Infections

E. faecalis
E. faecium
E. gallinarum
E. durans
E. avium
E. raffinosus
E. pallens
E. gilvus
E. cecorum
E. malodoratus
E. italicus
E. sanguinicola
E. mundtii
E. casseliflavus/flavescens
E. dispar
E. hirae
E. pseudoavium

methods or rapid biochemical methods such as the analytical profile index system, which appear to be accurate for *E. faecalis,* but not for other enterococcal species. Because *E. faecium* is capable of fermenting arabinose, some selective arabinose-containing agars have been used to differentiate *E. faecium* from other clinically relevant enterococcal species.[11] In addition, several molecular techniques have been developed for species differentiation, although they are not used routinely by clinical laboratories; among the most popular, amplification of *ddl* genes,[12] amplification of or a probe for the *ace* gene,[13] and sequencing of the 16S ribosomal RNA (rRNA) gene appear to reliably differentiate the relevant enterococcal species. Automated nucleic acid hybridization–based rapid diagnostic technologies and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry are now being used more commonly in the clinical microbiology laboratory; these techniques use species-specific sequence variation or protein fragment profiles to quickly identify *E. faecalis* and *E. faecium*. Furthermore, resistance to ampicillin usually indicates *E. faecium,* whereas nonsusceptibility to quinupristin-dalfopristin (Q-D) is usually seen in *E. faecalis.*

COLONIZATION, VIRULENCE, AND GENOMICS

Enterococci have well-adapted mechanisms to survive in the GI tract of humans. The human colonic microbiota comprises approximately 10^{13} commensal bacteria per gram of contents, encompassing more than 100 culturable bacterial species and many more nonculturable species, with a predominance of anaerobes.[14] Enterococci are clearly a minor population in relation to the anaerobic commensals in a normal host; they also appear to have a symbiotic relationship with the immune system and the other bacteria. However, one of the main effects that antibiotics have in the human gut is to alter the dynamics of colonization in favor of enterococci, which are naturally tolerant to a number of antimicrobial compounds (see "Therapy and Antimicrobial Resistance" later). Antibiotics that are excreted in the bile or have substantial antianaerobic activity without inhibiting enterococci (e.g., certain cephalosporins) have been shown to dramatically increase colonization of the GI tract by enterococci (e.g., vancomycin-resistant enterococci [VRE]).[15,16,17] Moreover, administration of broad-spectrum antibiotics favors VRE colonization of the murine GI tract in part by downregulating the intestinal expression of the antimicrobial peptide RegIIIγ (a bactericidal lectin produced by intestinal epithelial and Paneth cells), which has activity against gram-positive intestinal organisms. This effect appears to be due to the fact that broad-spectrum antibiotics suppress gram-negative organisms (including anaerobes) in the gut that are responsible for the activation of the signals necessary for the production of the RegIIIγ peptide through the lipopolysaccharide present in their outer membranes.[18] Moreover, the dominance of enterococci (particularly VRE) in the GI tract of hospitalized neutropenic patients after the administration of antibiotics has been shown to be a predictor of subsequent bloodstream infection in these patients.[19] Intestinal colonization of VRE also seems to be influenced by the presence of specific bacterial species of the gut anaerobic microbiota. Microbiota containing *Barnesiella* species conferred resistance to the domination by VRE in mice[20]; the presence of this species also correlated with decreased GI VRE colonization of patients undergoing allogeneic hematopoietic stem cell transplantation and receiving antibiotics.[20] A consortium of bacteria isolated from ampicillin-treated mice resistant to VRE colonization highlighted the complexity of unraveling the contributions of individual species within the microbiome. *Blautia producta,* a commensal anaerobe, directly inhibited VRE growth in the mouse GI tract after oral challenge; however, this inhibitory action depended on the presence of *Clostridium bolteae*. Furthermore, the β-lactamase–producing anaerobes *Bacteroides sartorii* and *Parabacteroides distasonis* were also required, presumably to clear inhibitory concentrations of ampicillin from the local environment and allow *B. producta* to proliferate.[21] Greater understanding of the interplay between the organisms in the microbiome and the host may allow for the therapeutic use of beneficial microbial cocktails to prevent VRE colonization in high-risk patients. Another factor that may also play a role in colonization and overgrowth of enterococci in the gut is increased stomach pH, usually secondary to the administration of proton pump inhibitors, a strategy commonly used in critically ill patients to reduce the incidence of aspiration pneumonitis.[22]

Considerable research has been performed in the investigation of pathogenic determinants that increase the ability of enterococci to cause disease by enhancing their virulence, survival, or colonizing capacity in human hosts. The cytolysin hemolysin is a bacterial toxin, often encoded by pheromone-responsive plasmids, that is capable of lysing eukaryotic (and prokaryotic) cells and has been shown to contribute to *E. faecalis* virulence.[23] Gelatinase and serine protease are bacterial enzymes that contribute to virulence in *E. faecalis*[24] by several potential mechanisms that include, among others, (1) facilitation of microbial invasion by altering immunoglobulins or complement molecules; (2) processing of virulence factors to regulate autolysis and release of high-molecular-weight extracellular DNA, a critical component for the development of *E. faecalis* biofilms[25]; and (3) degradation of host connective tissues, exposing ligands for bacterial attachment and possibly providing nutrients for the cell. The expression of gelatinase and serine protease genes is regulated by *fsr,* a two-component quorum-sensing global regulatory system that is similar to the *agr* system of *Staphylococcus*

aureus.[26,27] Gls24 of *E. faecalis* and Gls20/Gls33 of *E. faecium* are thought to be general stress proteins that have been shown to be important in virulence in both mouse peritonitis[28,29] and rat endocarditis[30] models. Although their function has not been fully elucidated, they are associated with resistance of enterococci to bile salts, and their homologues in *S. aureus* have been linked to upregulation of VraSR and PrsA, important members of the cell wall stress response.[31] Using comparative genome analysis, a locus encoding a putative phosphotransferase system was shown to increase the ability of *E. faecium* to colonize the murine intestinal tract during antibiotic treatment, and this system has been implicated in both biofilm formation and pathogenesis in a rat model of endocarditis.[32,33]

Cell surface components are important factors in bacterial virulence because they are usually the first molecules to interact with the host tissue or immune system or both. Aggregation substance of *E. faecalis* is encoded by pheromone-responsive plasmids and assists in a particular type of conjugative plasmid transfer as well as contributing to virulence (i.e., endocarditis). Aggregation substance proteins increase the adherence and internalization of enterococci into several eukaryotic cells (phagocytes, renal cells, intestinal cells, and epithelial cells) and enhance adherence of producing bacteria to serum and extracellular matrix proteins such as fibrin, fibronectin, thrombospondin, vitronectin, and collagen type I.[34] The *E. faecalis* surface protein (Esp) is another property found in some strains (and its homologue in *E. faecium*); it is a protein that appears to function as an adhesin involved in the formation of biofilms in a glucose-dependent manner.[35] Ace (adhesin to collagen of *E. faecalis*) belongs to the family designated as MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) and is considered part of the *E. faecalis* core genome. The Ace protein binds to collagen via what has been called the collagen hug model, in which the protein embraces the collagen molecule after initial docking.[36] A similar protein, Acm, identified in *E. faecium,* is important in the pathogenesis of endocarditis and implicated in the emergence of *E. faecium* as an important nosocomial pathogen.[37]

Another surface protein found to be important in enterococcal pathogenesis is ElrA (enterococcal leucine-rich repeat-containing protein). This polypeptide is a member of the WxL family of surface proteins, and deletion of the encoding gene attenuated *E. faecalis* virulence in a mouse peritonitis model.[38] The characterization of pili on the surface of gram-positive bacteria has been a major step in the understanding of bacterial virulence. In *E. faecalis,* the presence of pili (Ebp) was demonstrated (see Fig. 200.1), and the characterization of *ebp* genes encoding the pilus subunits led to establishing that these structures play a major role in biofilm formation and fibrinogen adhesion and are important in the pathogenesis of experimental endocarditis and urinary tract infections (UTIs).[39,40] Genes encoding homologous pilus subunits have also been identified in *E. faecium,*[41] indicating that the pili are ubiquitous structures of enterococci.

Polysaccharides on bacterial surfaces may be important pathogenic determinants and may affect leukocyte-mediated killing of bacteria. Certain *E. faecium* strains are resistant to polymorphonuclear cell killing, a characteristic that might be due to a carbohydrate-containing surface moiety.[42] In addition, antibody to a capsular polysaccharide component purified from an *E. faecalis* strain enhanced phagocytosis and killing of some strains of both *E. faecalis* and *E. faecium;* the capsular material may have vaccine potential because a reduction in bacterial numbers recovered from different organs of immunized mice was obtained compared with nonimmunized control subjects.[43,44] Using rabbit antisera for the typing of *E. faecalis,* four capsular serotypes (1, 2, 4, and 7) were found to be present in most clinical isolates,[45] and at least two types of gene clusters for the production of polysaccharide have been characterized (designated *epa*[46] and *cps* loci[47]). Passive immunization with antibodies against *E. faecalis* lipoteichoic acid promoted the clearance of *E. faecalis* bacteremia in mice. The antibodies bound lipoteichoic acid from other gram-positive organisms and opsonized *Staphylocccus epidermidis, S. aureus,* and group B streptococci,[48] raising the possibility of using these antibodies for possible vaccine development.

In *E. faecium,* acquisition of a very large plasmid (approximately 250 kb) by a commensal strain increased the virulence of the organism in a mouse peritonitis model.[49] These virulence plasmids have been highly associated with clinical strains versus commensal isolates.[50] More recently, genes associated with the regulation of oxidative stress have been identified as important in the virulence of *E. faecium*. One of these regulators is AsrR, which uses cysteine oxidation to sense hydrogen peroxide mediating the activation of many genes potentially involved in pathogenesis (e.g., *acm*), antibiotic and antimicrobial peptide resistance, oxidative stress, and adaptive responses. Among the genes regulated by AsrR was *pbp5*, encoding a low-affinity penicillin-binding protein 5 (PBP5); deletion of *asrR* markedly decreased the bactericidal activity of ampicillin and vancomycin and increased the ability of the mutant to form biofilm and persistence in *Galleria mellonella* and mouse systemic infection models.[51]

Sequencing of enterococcal genomes has been another useful tool to facilitate the understanding of the complicated pathway by which enterococci evolved from commensals to pathogens. Sequencing of the genome of the first vancomycin-resistant *E. faecalis* strain isolated in the United States (designated V583) indicated that more than one-quarter of its genome is mobile DNA. A pathogenicity island, which is a large genetic element carrying a set of putative virulence-associated genes,[52] a transposon carrying the *vanB* gene cluster, three plasmids with antibiotic-resistance determinants, and insertion sequences were the most prominent, potentially mobile elements of V583.[53] The pathogenicity island encodes factors that may enable enterococci to gain an advantage in the gut, such as the cytolysin that has antibacterial properties, several surface adhesins, several carbohydrate utilization pathways, and enzymes that may permit colonization of certain areas of the intestine. It has been postulated that this pathogenicity island was acquired by an ancestral *E. faecalis* clonal strain that evolved to acquire antibiotic resistance determinants, thus becoming equipped to cause problematic infections in humans. Importantly, V583 and other multidrug-resistant strains lack an active CRISPR (clustered regularly interspaced short palindromic repeats)/Cas system, which acts as an immune system protecting the bacterial cell from incoming foreign DNA (i.e., phages). This deficiency has been associated with an increased frequency of mobile DNA elements (including plasmids and transposons), which can carry resistance determinants and may explain their nosocomial predominance.[54] Similarly, sequencing of the entire genome of another *E. faecalis* strain (*E. faecalis* OG1RF) revealed considerable variation in gene content in this species. As opposed to V583, *E. faecalis* OG1RF lacks plasmids and the pathogenicity island but is still able to cause infection in animal models. This strain has an intact CRISPR/Cas system and lacks the mobile elements typical of V583 but harbors genes predicted to encode proteins involved in adherence, defense against bacteriophages, metabolism of *myo*-inositol, and novel surface proteins.[55] Recent genome comparisons indicate that there are two ancestrally distinct clades of *E. faecium* (animal and human commensal)[56,57] that diverged from each other at least thousands of years ago; a third subclade responsible for most human, health care–associated *E. faecium* infections is estimated to have evolved from the animal clade approximately 75 years ago, coinciding with the time that antibiotics were introduced in clinical medicine to become successful in the nosocomial environment.[56–58] This hospital-associated *E. faecium* clade, which mostly contains clinical and outbreak-associated strains, characteristically contains *pbp5-R,* the allele encoding the ampicillin-resistant version of PBP5, and insertion sequences, such as IS*16*.

EPIDEMIOLOGY OF ENTEROCOCCAL INFECTIONS

The two most common species responsible for the vast majority of enterococcal infections are *E. faecalis* and *E. faecium.* The only other species of enterococci known to be responsible for outbreaks and nosocomial spread, albeit rare, is *E. gallinarum.*[59] Taken together, enterococci were the third leading cause of nosocomial infections in the United States from 2011 to 2014, with VRE now accounting for approximately 30% of enterococcal infections with most VRE isolates being *E. faecium* (>90%).[60] The first step in the infectious process appears to involve colonization of the GI tract by hospital-associated strains, which may persist for months or years, although direct inoculation onto intravenous or urinary catheters, onto intravenous stop-cock sets, or via thermometers has been reported. The hospital environment can be heavily colonized

with VRE, including bed rails, linen, doorknobs, bedpans, urinals, blood pressure cuffs, stethoscopes, and monitoring equipment, among others.[61] Risk factors associated with increased VRE colonization include the presence of immunosuppression or serious comorbid conditions (e.g., diabetes, renal failure, high Acute Physiology and Chronic Health Evaluation [APACHE] score); increased length of hospital stay; residence in a long-term care facility; proximity to another colonized or infected patient, including sharing a room or hospitalization in a room previously occupied by a patient colonized with VRE; and invasive procedures and administration of broad-spectrum antibiotics (e.g., cephalosporins), antianaerobic drugs (e.g., metronidazole), or vancomycin.[62,63] The hands of health care workers seem to be the most common source of transmission of VRE, and the Society for Health Epidemiology of America has published specific guidelines to curtail this transmission.[64] The organisms are capable of surviving on the hands, gloves, and gowns of health care workers for prolonged periods, and independent risk factors for glove and gown contamination include contact with a colonized patient's catheter or drain, trunk, or lower extremity.[65]

Once a patient becomes colonized with VRE, the risk of developing a subsequent bloodstream infection with the same VRE-colonizing strain appears to increase,[66] although some studies have not found an association. Rates of bloodstream infections in patients colonized with VRE range from 0% to 34% and seem to be higher among patients with cancer and solid-organ and bone marrow transplant recipients. Risk factors associated with developing a VRE bloodstream infection in a patient already colonized with VRE include cancer or diabetes (relative risk [RR], 3.91), GI procedures (RR, 4.56), acute renal failure (RR, 3.1), exposure to vancomycin (RR, 1.95), infection of a site other than blood (odds ratio, 3.9),[67] and dominance of VRE in the GI tract following use of broad-spectrum antibiotics.[19] Among patients with leukemia, concurrent *Clostridioides difficile* (formerly *Clostridium difficile*) infection was associated with increased risk of developing a VRE bloodstream infection.[68] In addition, two meta-analyses evaluated the mortality of patients with VRE bacteremia compared with patients with vancomycin-susceptible enterococci (VSE).[69,70] Both studies concluded that patients with bacteremia due to VRE were approximately 2.5 times more likely to die than patients with VSE bacteremia, indicating that the development of vancomycin resistance is a poor prognostic sign in critically ill patients. Despite the introduction of antibiotics with in vitro bactericidal activity against VRE, such as daptomycin, this effect persists, with data showing VRE bacteremia associated with an increase in mortality (odds ratio, 1.8) and longer hospital stays (mean 5.01 days) compared with VSE bacteremia.[71]

CLINICAL MANIFESTATIONS OF ENTEROCOCCAL DISEASE

Bacteremia and Endocarditis

Bacteremia and infective endocarditis (IE) are common presentations of enterococcal disease. Bacteremia without endocarditis is by far the more frequent presentation, and enterococci are one of the leading causes of nosocomial bacteremias.[60] Frequent sources of the bacteremia are the genitourinary and GI tracts in patients with infections originating outside the hospital (endocarditis should always be ruled out). Intravascular or urinary catheters are the most common sources of nosocomial bacteremia, and intraabdominal, pelvic, biliary tract, wound (including in burned patients), and bone infections have also been documented as sources of bacteremia. Enterococcal bacteremia often occurs in debilitated patients who have received antibiotics and have serious underlying conditions, and polymicrobial bacteremia can be seen in approximately 50% of cases; however, polymicrobial bacteremia has not been independently associated with mortality.[72,73] Data suggest that *E. faecium* bloodstream infections may have a worse prognosis than *E. faecalis,* probably because these organisms are much more resistant to antibiotics and are increasingly difficult to treat.[74] Enterococcal bacteremia and meningitis (see "Meningitis") have also been associated with the *Strongyloides* hyperinfection syndrome (see Chapter 286).[75]

The percentage of patients who have endocarditis as the cause of detectable enterococcal bacteremia varies according to the study and population studied, ranging from about 1% to 32%. Enterococci are the second (after staphylococci) most common cause of health care–associated endocarditis and third (after staphylococci and streptococci) most common cause of endocarditis in the community setting depending on the series and patients examined, accounting for 5% to 20% of cases of endocarditis. In a worldwide observational cohort study that included 2781 patients with endocarditis, enterococci were the third most common etiologic agents after *S. aureus* and streptococci, with a higher incidence in North America compared with other regions of the world.[76] Factors independently associated with IE in 647 patients presenting with *E. faecalis* bacteremia included monomicrobial cultures with *E. faecalis* (hazard ratio [HR], 3.6), prosthetic heart valve (HR, 6.2), male sex (HR, 2.0), and community acquisition (HR, 1.8).[77] The NOVA score, a scoring system used to identify patients with predominately *E. faecalis* bacteremia at low risk of IE in whom transesophageal echocardiography could be deferred, has been validated using an external cohort.[77,78] The criteria include three of three positive blood cultures (or the majority if more than three blood cultures obtained; 5 points), unknown origin of bacteremia (4 points), prior valvular disease (2 points), and presence of a heart murmur (1 point), with patients receiving a score <4 at low risk of IE. Although the majority of the validation cohort with IE had a score ≥4 (97%), clinical judgment and an index of suspicion should still be used to guide performing transesophageal echocardiography in select patients.

Enterococci can affect both native and prosthetic valves and can cause both community-acquired and nosocomial endocarditis, with *E. faecalis* being recovered much more frequently than *E. faecium* or other enterococcal species. The disease usually occurs in the setting of damaged heart valves, and the mitral and aortic valves are usually involved, although endocarditis of apparently intact valves also occurs.[79,80] Most patients tend to be male and elderly with comorbidities, although enterococcal endocarditis in women of childbearing age has been well documented. The infection usually originates from the genitourinary or GI tract. Procedures associated with the development of enterococcal endocarditis include cystoscopy, cesarean section, prostatectomy, transrectal prostatic biopsy, transjugular intrahepatic portosystemic shunt, extracorporeal shock wave lithotripsy, colonoscopy, fiberoptic sigmoidoscopy, and liver biopsy.[7,80] Malignant and inflammatory lesions of the gut and biliary tract may also be the source of endocarditis.[81]

Most patients with enterococcal endocarditis display a subacute course, and the most common clinical manifestations include fever; presence of a murmur; and constitutional symptoms such as weight loss, generalized aches, and malaise. Peripheral signs of endocarditis such as petechiae, Osler nodes, and Roth spots have been found less frequently (approximately 15%) than in endocarditis caused by other organisms.[80] Atypical manifestations include polyarthritis,[82] spondylodiskitis,[83] metastatic abscesses in the spleen,[84] and empyema.[85] The most common complication of enterococcal endocarditis is heart failure, which occurs in about half of patients, with a significant percentage requiring valve replacement. Embolization occurs in 27% to 43% of patients,[80,86] and the brain appears to be the most common end organ. Mortality ranges from 11% to 35%; in a cohort of 500 patients with confirmed enterococcal endocarditis, increasing age (HR, 1.02 per 1-year increment), heart failure (HR, 2.43), and stroke (HR, 1.9) were all associated with an increase in 1-year mortality.[87]

Urinary Tract Infections

Enterococcal UTI in young healthy women without a history of urinary tract instrumentation or anatomic abnormalities is infrequent (<5% of all UTIs) and was first reported in 1906.[3] Conversely, enterococcal UTIs are well documented in the hospital and usually associated with indwelling catheters, instrumentation, and abnormalities of the genitourinary tract. Data from the Centers for Disease Control and Prevention National Healthcare Safety Network from 463 hospitals across the United States indicate that enterococci are the fifth most common organism isolated from catheter-associated UTIs, with *E. faecium* and *E. faecalis* accounting for the majority of organisms isolated.[60] It is sometimes difficult to differentiate between infection and colonization in the hospital setting; therefore the isolation of greater than 10^5 colony-forming units of *Enterococus* spp. from urine may represent colonization, and removal of the catheter may suffice to eradicate the presence of the organism. Recurrent UTIs and previous antibiotic treatment have also

been associated with enterococcal UTIs. The infection appears to be more common in older men, and associated prostatitis or epididymitis have been documented. Enterococci can also cause complicated UTIs (although less frequently than *Escherichia coli*), with the development of pyelonephritis and perinephric abscesses that can lead to bacteremic episodes.[7]

Meningitis

Enterococci are uncommon causes of meningitis, accounting for approximately 0.3% to 4% of meningitis cases according to different series.[88,89] Two presentations are usually described: spontaneous and postoperative meningitis. *E. faecalis* is the most common species isolated, followed by *E. faecium, E. gallinarum, E. avium,* and *E. casseliflavus*. Spontaneous meningitis is a community-associated infection that often manifests in patients with severe comorbidities such as diabetes, chronic renal failure, pulmonary or cardiovascular disease, immunosuppression (including steroid use and human immunodeficiency virus), malignancies, transplantation, and splenectomy. In approximately 15% of cases, meningitis can manifest in apparently healthy individuals with no clear focus of infection.[89,90] In children, spontaneous meningitis has been reported in association with central nervous system (CNS) pathology (neural tube defects and hydrocephalus), prematurity, recent surgery, or congenital heart disease. Meningitis in the setting of disseminated strongyloidiasis has also been well characterized. Postoperative meningitis is a hospital-associated infection, and the presence of shunt devices appears to be the most important predisposing factor. Enterococcal meningitis has rarely been reported as a complication of lumbar or ventricular tap, placement of CNS electrodes, and epidural anesthesia.[89]

The clinical characteristics of meningitis are similar in patients with spontaneous and postoperative presentations. Patients have an acute course with fever, altered mental status, and signs of meningeal irritation; in some cases, coma, petechial rash, shock, and focal CNS deficits may develop. Cerebrospinal fluid (CSF) findings include pleocytosis, increased protein levels, and low glucose. In a series of 140 patients with enterococcal meningitis, the median CSF leukocyte count was 533 mm^3, and only 35% of patients had a leukocyte count of less than 200 mm^3, with a positive Gram stain seen in up to 40% of patients.[89] Accompanying bacteremia can be found in more than half of cases of spontaneous meningitis. Complications of enterococcal meningitis include hydrocephalus, stroke, and brain abscesses. The overall mortality approaches 20%, and poor prognostic factors include seizures, altered consciousness, advanced age, respiratory failure, septic shock, and the presence of hypoglycorrhachia or decreased white blood cell count in the CSF[88]; residual sequelae in approximately 17% of patients[89] were reported in one study.

Intraabdominal and Pelvic Infections

Enterococci are commensals of the GI and genitourinary tracts and are commonly isolated from abdominal and pelvic infections, usually with gram-negative and anaerobic organisms; the role of enterococci in these infections is controversial.[91] An analysis of six clinical trials with the objective of examining the use of antibiotics without enterococcal activity in the treatment of intraabdominal infections did not find any case of treatment failure, despite evidence of the presence of enterococci in 20% to 30% of initial cultures.[92] Similarly, several studies have shown that community-associated complicated intraabdominal infections with mixed microbiota that include enterococci can be treated with surgery and antibiotics that do not exhibit in vitro activity against enterococci. Moreover, data from animal experiments indicate that enterococci alone do not cause intraabdominal sepsis when injected intraperitoneally, unless other substances or organisms that promote abscess formation are added.[93] Nonetheless, several well-conducted studies have demonstrated that enterococci can cause treatment failures and adverse outcomes; a randomized, prospective, double-blind trial comprising 330 patients concluded that the isolation of enterococci from intraabdominal collections was a predictor of treatment failure.[94] Several other series confirmed these observations, concluding that the presence of enterococci increases postoperative infectious complications and mortality in these patients.

The bulk of evidence indicates that the use of antienterococcal antibiotics may not be necessary for initial treatment of acute intraabdominal infections in most cases. However, the apparent increased frequency of isolation of nosocomial multidrug-resistant enterococci indicates that antienterococcal therapy should be considered for immunocompromised and severely ill patients with nosocomial peritonitis and abdominal sepsis or persistent collections who have received broad-spectrum antibiotics that do not have activity against enterococci (e.g., cephalosporins) as well as patients with peritonitis and damaged or prosthetic heart valves (to prevent endocarditis).[91] Enterococci are also capable of producing spontaneous peritonitis and empyema in cirrhotic patients and patients with chronic renal failure and have been reported as etiologic agents in peritonitis associated with chronic ambulatory peritoneal dialysis.[7]

Neonatal Infections

Enterococci are part of the normal adult vaginal microbiota and can be acquired by neonates during delivery. Although carriage of enterococci is common, colonization with VRE is rare; it was found in about 1% in a multicenter study of 1320 infants.[95] The organisms have been implicated in approximately 6% of late-onset sepsis cases, 5% of pneumonias, 9% of surgical site infections, 10% of bacteremias, 17% of UTIs, and 6% of meningitis cases in neonatal units.[96,97] In cases of late-onset sepsis, enterococcal infections are usually nosocomial and may be polymicrobial. Affected patients usually have had a prolonged hospital stay, low birth weight, prior antibiotic therapy, and several invasive procedures. The clinical presentation of sepsis is usually associated with localized sites of infection or necrotizing enterocolitis. Endocarditis is rare in the neonatal period but can be seen in infants with prolonged enterococcal bacteremia.[96]

Several outbreaks of neonatal sepsis have been documented in the literature. In 1982, an outbreak of *E. faecium* was documented in Virginia[98]; the infants had severe underlying conditions, with the presence of endovascular devices and nasogastric tubes, and were premature. Similarly, a 6-month outbreak of *E. faecalis* neonatal sepsis was documented in Colorado in 1987; most of the infants were also premature, with low birth weight, and had intravascular devices and had undergone bowel surgery.[99] Outbreaks of VRE causing sepsis in neonates have also been well characterized in different parts of the world.

Skin, Soft Tissue, and Other Infections

Enterococci have been associated with skin and soft tissue (including wound) infections. When found in clinical samples from soft tissues, they are usually accompanied by other microorganisms; therefore their pathogenic role in these infections is unknown. Decubitus and diabetic foot ulcers are the usual lesions associated with the presence of enterococci; in some cases the organisms have been isolated from bone affected by osteomyelitis.[100] The simultaneous presence of vancomycin-resistant *E. faecalis* and *S. aureus* in diabetic wound infections has been associated with the transfer of the *vanA* gene cluster (encoding proteins necessary for vancomycin resistance) from enterococci to *S. aureus*.[101] Enterococci are rare causes of soft tissue abscesses; however, liver, lung, and brain abscesses have been reported.[102] The authors have seen a breast abscess caused by *E. faecium* in a patient hospitalized in the critical care unit. Enterococcal pneumonia and spontaneous empyema are also uncommon but have been occasionally described.

THERAPY AND ANTIMICROBIAL RESISTANCE

The main hurdle the clinician faces in the treatment of enterococcal infections is that these organisms are intrinsically resistant to a number of compounds and have an ability to acquire antibiotic-resistance genes. These therapeutic problems have long been recognized; in the past, approximately 60% of failures in the treatment of enterococcal endocarditis occurred when penicillin was used as monotherapy,[7] as opposed to endocarditis caused by streptococci. Bactericidal therapy is needed for optimal cure rates in endocarditis and other endovascular infections, which is usually not achieved with available single agents; therefore combination therapy should usually be given (Figs. 200.2 and 200.3; Table 200.3). The emergence of resistance to various antimicrobial agents seen commonly in *E. faecium* poses enormous clinical problems because the goal of bactericidal therapy often cannot be achieved.

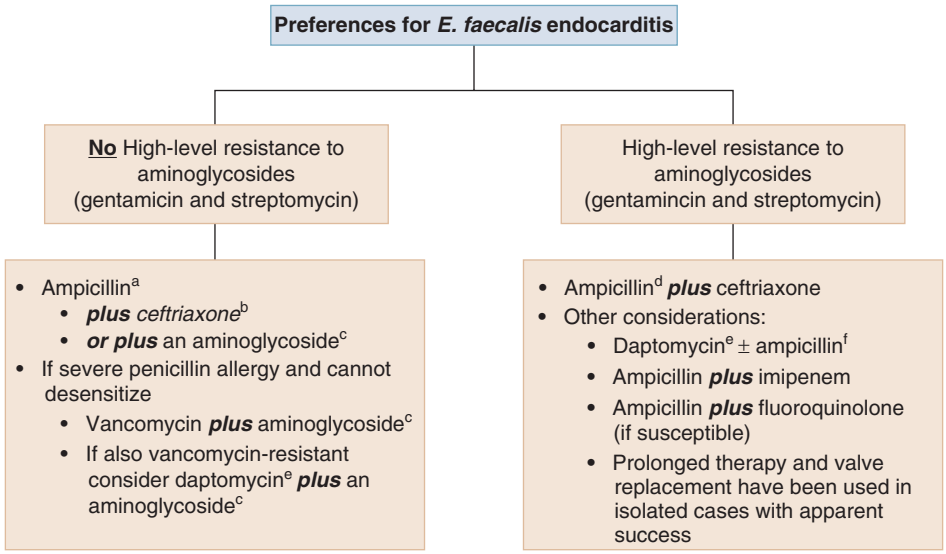

FIG. 200.2 Possible therapeutic alternatives for the treatment of endocarditis caused by *enterococcus faecalis*. [a]In rare cases of β-lactamase–producing isolates, the American Heart Association (AHA) recommends ampicillin-sulbactam 12 g/day. [b]The AHA recommends ampicillin plus ceftriaxone for patients whose creatinine clearance is <50 mL/min. [c]Gentamicin or streptomycin (see text); the AHA recommends gentamicin administered at 3 mg/kg/day in two or three divided doses. Data are insufficient to recommend once-daily dosing regimens for enterococcal endocarditis in patients with normal renal function. [d]Continuous infusion of ampicillin or ampicillin-sulbactam as monotherapy is preferred by some. [e]High-dose daptomycin (8–12 mg/kg) is preferred. [f]Addition of another active agent (e.g., ampicillin, ceftaroline) might be considered. None of these uses are approved by the US Food and Drug Administration, and prospective, randomized trials have not been conducted. Recommendations are based on literature review and personal opinion. Therapy duration is generally 6 weeks for both native and prosthetic valve endocarditis; 4 weeks of ampicillin plus an aminoglycoside appears to suffice for native valve endocarditis of less than 3 months' duration. Longer durations of therapy should be considered when neither a β-lactam nor vancomycin can be used. *(Modified from Arias CA, Contreras GA, Murray BE. Management of multidrug-resistant enterococcal infections.* Clin Microbiol Infect. *2010;16:555–562.)*

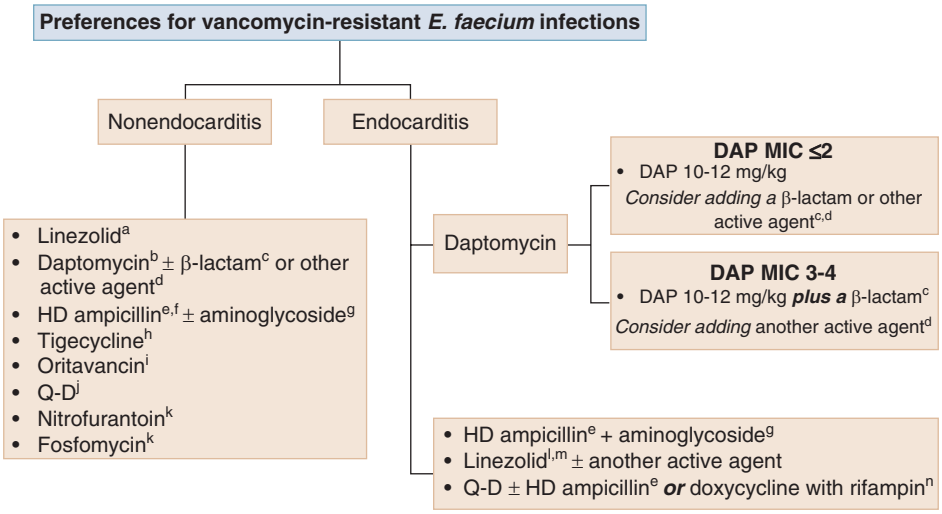

FIG. 200.3 Possible therapeutic alternatives for treatment of infections caused by vancomycin-resistant *enterococcus faecium*. [a]Linezolid is approved by the Food and Drug Administration (FDA) for nonendocarditis vancomycin-resistant *E. faecium* infections. Linezolid, daptomycin, and quinupristin-dalfopristin *(Q-D)* (the latter two also used intrathecally) have been successfully used against meningitis caused by vancomycin-resistant isolates of *E. faecium*. [b]Use of high-dose *(HD)* daptomycin (8–12 mg/kg) is preferable to 6 mg/kg. [c]In vitro data suggest that ampicillin, ceftaroline, and ertapenem are reasonable choices as additive or synergistic β-lactam therapy. [d]Other potentially active agents include (there is need to confirm with in vitro susceptibilities) tigecycline, fluoroquinolones, Q-D, or an aminoglycoside (gentamicin or streptomycin). [e]If minimal inhibitory concentration *(MIC)* is ≤64 μg/mL, HD ampicillin up to 30 g/day could be considered. However, toxicity at high ampicillin doses has not been systematically assessed. HD ampicillin *plus* imipenem (for imipenem MIC ≤32 μg/mL) is a consideration if high-level resistance to aminoglycosides is present. [f]Because of high urine concentrations obtained with ampicillin therapy, ampicillin is likely to be effective in lower urinary tract infections, even when caused by organisms with MICs ≥128 μg/mL (*plus* catheter removal). [g]If the organism lacks high-level resistance to gentamicin or streptomycin. [h]Not approved for any *E. faecium* infection but active in vitro; concerns exist in treatment of bacteremia because of low tigecycline serum levels, although it may have a role in combination therapies (e.g., with daptomycin) against multidrug-resistant *E. faecium*. It has favorable pharmacokinetics in intraabdominal tissues. [i]Case report of prosthetic valve endocarditis, initial dosing was 1200 mg every other day for three doses, then once weekly for 6 weeks. The dosing interval was increased to twice weekly after the patient experienced a relapse. Mild transaminitis and elevation of alkaline phosphatase was reported at 10 weeks on a twice-weekly dosing regimen. [j]Q-D was the first agent approved by the FDA for vancomycin-resistant enterococci (VRE), but this indication has since been withdrawn. Q-D has been used both systemically and as intrathecal therapy for VRE meningitis. [k]Urinary tract infections only. [l]Linezolid and daptomycin are listed in the American Heart Association/Infectious Diseases Society of America recommendations for the treatment of vancomycin and ampicillin-resistant *E. faecium*. [m]Concerns over reports of lack of efficacy or development of resistance with monotherapy. [n]If susceptible to each agent. The recommendations for compounds that are not FDA-approved are based on literature review and personal opinion. No prospective, randomized trials have been conducted. *(Modified from Arias CA, Contreras GA, Murray BE. Management of multidrug-resistant enterococcal infections.* Clin Microbiol Infect. *2010;16:555–562.)*

TABLE 200.3 Treatment of Nonendovascular Infections Caused by β-Lactam and Glycopeptide-Susceptible Enterococcal Species

DISEASE	SUGGESTED REGIMEN	DOSAGE AND DURATION (NORMAL RENAL AND LIVER FUNCTIONS)
Bacteremia[a]	Ampicillin[b] *or* Penicillin G *or* Vancomycin	9–12 g daily IV in divided doses q4–6h for 14 days[c] 18-30 million U IV daily divided q4–6h for 14 days[c] 30 mg/kg daily IV in divided doses for 14 days[c]
Meningitis[d]	Ampicillin[e] *or* Penicillin G[e] *plus* Ceftriaxone[f] *plus* Gentamicin[g] *or* Streptomycin	2 g q4h IV for 14 days 4 million U q4h IV for 14 days 2 g IV q12h 2 mg/kg loading dose, followed by 1.7 mg/kg IV q8h *or* 3 mg/kg IV q24h 7.5 mg/kg body weight q12h (evaluation of drug levels is strongly recommended) for 14 days
Urinary tract infections	Nitrofurantoin Fosfomycin Amoxicillin[h]	100 mg PO q6h for 5 days 3 g PO (single dose) 875 mg to 1 g PO q12h for 5 days

[a]Adding an aminoglycoside for synergistic therapy (gentamicin, 1 mg/kg q8h, or streptomycin, 7.5 mg/kg q12h) with a cell wall agent should be considered in seriously ill patients or patients with high risk of developing endocarditis, as indicated in Fig. 200.2. Adding ceftriaxone to ampicillin is an alternative to aminoglycosides.
[b]In rare β-lactamase–producing isolates, ampicillin-sulbactam (12 g daily in divided doses) should be considered.
[c]In catheter-associated bacteremias, a shorter duration of therapy (5–7 days) may be sufficient after removal of the catheter.
[d]In refractory cases, linezolid has been reported to be successful; intrathecal vancomycin, daptomycin, or gentamicin may be considered in cases of postoperative meningitis or with failure to respond to systemic antibiotics.
[e]For patients with penicillin allergy, intravenous vancomycin, 15–20 mg/kg q8–12h (adjust dosage to achieve vancomycin serum trough concentrations of 15–20 μg/mL), is recommended.
[f]Ampicillin plus ceftriaxone, along with the addition of an aminoglycoside (if no high-level resistance to aminoglycosides is present), may be considered for treatment of meningitis.
[g]Once-daily dosing of gentamicin may be considered in this context. Clinical data are not available, but the higher peak level of the extended interval dosing regimen may facilitate drug penetration to the cerebrospinal fluid.
[h]For bacteria that produce β-lactamase, amoxicillin-clavulanate can be used.
IV, Intravenously; *PO,* per os (orally).

Combination of β-Lactam and Aminoglycosides or Cephalosporins

β-Lactam antibiotics inhibit the penicillin-binding proteins of susceptible bacteria, thus interfering with cell wall synthesis, and this class of antibiotics should be the first choice for the treatment of susceptible enterococcal isolates (see Table 200.3). Relative resistance to β-lactams with minimal inhibitory concentrations (MICs) of penicillin 10 to ≥100 times those of streptococci is a well-described characteristic of enterococci. Many strains are also tolerant to β-lactams, that is, not killed with concentrations of antibiotics ≥16 times higher than the MIC.[103] The most potent activity is observed with the aminopenicillins (e.g., ampicillin) and ureidopenicillins, followed by penicillin G and imipenem. Although the MIC breakpoint defined by the Clinical and Laboratory Standards Institute for ampicillin resistance is ≥16 mg/L, high doses of ampicillin can achieve plasma concentrations ≥150 mg/L, which has led to the suggestion that isolates with ampicillin MICs ≤64 mg/L might be successfully treated with doses of 18 to 30 g/day of ampicillin or ampicillin-sulbactam[104] usually combined with an aminoglycoside (see later), although there are few safety data for use of this high-dose β-lactam regimen.

Resistance to penicillins and carbapenems is usually found in clinical isolates of *E. faecium* and rarely in *E. faecalis*. The mechanisms of resistance in *E. faecium* appear to involve the expression of a resistant *pbp5* allele (*pbp5-R*) (whose DNA sequence differs from that of susceptible *pbp5* by approximately 5%)[105] with decreased affinity for ampicillin.[106] Differences in the genetic environment of the *pbp5* gene correlated with increased expression of PBP5 in strains belonging to the ampicillin-resistant clinical clade (also known as health care–associated clade), suggesting factors other than amino acid sequence also play a role in PBP5-mediated resistance.[107] A laboratory strain of *E. faecium* with a penicillin-binding protein–independent mechanism of β-lactam resistance involving a novel transpeptidation pathway of peptidoglycan synthesis has also been reported,[108] although no clinical isolates have so far been found to exhibit this mechanism. β-Lactam resistance in *E. faecalis* can be mediated by the production of a β-lactamase enzyme[109]; although rare, occasional outbreak strains harboring this enzyme have been reported, mainly in the United States and Argentina. The presence of this enzyme is not detected by routine susceptibility testing, and therefore testing specifically for β-lactamase in endocarditis or serious enterococcal infections should be considered.[110] Some strains of *E. faecalis* have been found to be susceptible to ampicillin but resistant to penicillin and imipenem[111]; although the mechanism of this discrepancy on β-lactam susceptibility has not been demonstrated experimentally, decreased susceptibility correlates with specific amino acid changes in PBP4.

A bactericidal regimen should be used for the treatment of enterococcal endocarditis (see Figs. 200.2 and 200.3) and is recommended for any other endovascular infection. However, as mentioned before, β-lactams are not often bactericidal for enterococci, but a synergistic and bactericidal effect is usually achieved with the addition of an aminoglycoside. In vitro, synergism in enterococci is defined as a ≥2 $\log_{10}$ increase in killing at 24 hours by the combination compared with the β-lactam (or glycopeptides; see later) alone when the concentration of the aminoglycoside does not have any effect on the growth curve of the microorganism, with a 99.9% decrease from the starting bacterial inoculum resulting from the antibiotic combination. Gentamicin and streptomycin are the only two aminoglycosides recommended for achieving this synergistic effect in clinical practice. The use of other aminoglycosides for this purpose is discouraged (see later).

High-level resistance (HLR) to aminoglycosides is defined by growth at concentrations of 2000 mg/L and 500 mg/L of streptomycin and gentamicin, respectively, on brain heart infusion agar or 1000 mg/L of streptomycin when using brain heart infusion broth. The presence of HLR to both gentamicin and streptomycin abolishes the synergistic effect of these compounds in clinical practice. The emergence of enterococci with HLR to both aminoglycosides was reported in 1983[112] and has increased since then in both *E. faecalis* and *E. faecium*. HLR to gentamicin is mostly due to the presence of a bifunctional aminoglycoside-modifying enzyme, AAC(6′)-IE-APH(2″)-Ia, that confers high-level resistance to gentamicin (as well as HLR or resistance to

synergism with tobramycin, netilmicin, sisomicin, kanamycin, and amikacin, but not streptomycin). HLR to streptomycin can be due to mutations in the 30S ribosomal subunit[113] and to the presence of a streptomycin adenylyltransferase.[112] Evaluation for the presence of HLR has been the standard of care for treatment of all enterococcal isolates causing endovascular or severe infections. As a caveat, rare isolates of both *E. faecalis* and *E. faecium* (and *E. gallinarum*) whose MICs of gentamicin are lower than 500 mg/L (i.e., reported as not HLR to gentamicin) may be resistant to the synergistic effect of the combination with a cell wall agent because of the presence of the APH(2″)-Ic enzyme or other, yet unidentified mechanisms. Hence this situation must be considered in patients who do not respond appropriately to combination therapy with aminoglycosides with isolates reported as not having HLR to aminoglycosides.

Aminoglycosides other than gentamicin and streptomycin are not recommended for the treatment of enterococcal infections (except possibly arbekacin and tobramycin in *E. faecalis,* with no HLR to gentamicin; see later) because (1) as stated earlier, the common mechanism of resistance to gentamicin in clinical isolates is mediated by the AAC(6′)-Ie-APH(2″)-Ia enzyme, which confers resistance to synergism with all aminoglycosides commonly available in the United States except streptomycin; (2) *E. faecium* (as a species characteristic) produces an aminoglycoside modifying enzyme, 6′-acetyltransferase (6′-AAC), that results in higher MICs of tobramycin as well as kanamycin, netilmicin, and sisomicin, resulting in loss of the synergistic effect with cell wall agents; and (3) the *aph(3′)-IIIa* gene (encoding a kanamycin/neomycin phosphotransferase) is commonly found in enterococci and confers HLR or resistance to synergism with amikacin and kanamycin. In Japan, the aminoglycoside arbekacin is approved for clinical use, and this compound appears to be more stable to the action of the AAC(6′)-Ie-APH(2″)-Ia enzyme. It has also been shown that arbekacin exhibited synergism in vitro when combined with ampicillin against 40% of enterococci possessing the bifunctional enzyme.[114] Therefore this compound may be useful for certain isolates with HLR to aminoglycosides.

Typically the cephalosporins have weak activity against all species of enterococci with two exceptions. First is ceftriaxone (or cefotaxime) in combination with ampicillin; this regimen was initially used for the treatment of endocarditis caused by isolates of *E. faecalis* exhibiting HLR to all aminoglycosides (see Fig. 200.2).[115,116] The rationale for this approach is based on the observation that low concentrations of an aminopenicillin may be capable of partially saturating low-molecular-weight PBP4 and PBP5, but not PBP2 and PBP3, which then could actively participate in the synthesis of the bacterial cell wall. The addition of cefotaxime (or ceftriaxone) could produce total saturation of PBP2 and PBP3 and result in a bactericidal synergistic effect[117] against *E. faecalis.* (This effect is not observed in clinical isolates of *E. faecium.*) In the initial open-label and nonrandomized trial in Spain, 43 patients with *E. faecalis* endocarditis were treated successfully (clinical cure rate at 3 months was 67.4%) with the combination of ceftriaxone (2 g every 12 hours) and ampicillin (2 g every 4 hours) given for 6 weeks.[115] A subsequent observational, nonrandomized, comparative multicenter cohort study at 17 Spanish hospitals and 1 Italian hospital compared ampicillin-gentamicin versus ampicillin-ceftriaxone combinations for *E. faecalis* endocarditis. There were no differences in mortality while on antimicrobial treatment (22% vs. 21%, $P = .81$) or at 3-month follow-up (8% vs. 7%, $P = .72$), in treatment failure requiring a change in antimicrobials (1% vs. 2%, $P = .54$), or in relapses (3% vs. 4%, $P = .67$). Interruption of antibiotic treatment because of adverse events (mainly because of increases in creatinine values) was much more frequent in the gentamicin arm than in patients receiving ampicillin plus ceftriaxone (25% vs. 1%, $P < .001$) (≥25% increase in baseline creatinine concentration; 23% vs. 0%, $P < .001$), indicating that ceftriaxone-ampicillin is a good alternative in patients at risk of aminoglycoside toxicity, if not the therapy of choice.[116]

Ceftobiprole and ceftaroline are examples of a new generation of cephalosporins with increased affinity for penicillin-binding proteins of many resistant species, mainly PBP2a of methicillin-resistant *S. aureus*, that have relatively good activity against clinical isolates of *E. faecalis,* but not ampicillin-resistant *E. faecium*.[118] Ceftobiprole has potent activity against β-lactamase–producing and vancomycin-resistant strains of *E. faecalis,* it has exhibited synergism with aminoglycosides against selected isolates of *E. faecalis,* and its activity was comparable to ampicillin in an in vivo mouse peritonitis model.[118]

Glycopeptides and Lipoglycopeptides

The two glycopeptides currently used in clinical practice to treat enterococcal infections are vancomycin and teicoplanin. The mechanism of action of these compounds includes the inhibition of the last steps of peptidoglycan synthesis, which involves transglycosylation and transpeptidation of the pentapeptide units. Glycopeptides have been mainly used in the past in the treatment of β-lactam–resistant *E. faecium.* However, the increased prevalence of vancomycin resistance (e.g., approximately 80% of *E. faecium* isolates in the United States are resistant to vancomycin) has reduced the clinical use of these compounds against enterococci. Oritavancin is a semisynthetic glycopeptide antibiotic derived from chloroeremomycin and approved for acute bacterial skin and skin structure infections including vancomycin-susceptible isolates of *E. faecalis*, but not VRE. In vitro, oritavancin has potent dose-dependent bactericidal activity against enterococci including VRE with MICs ranging from 1 to 2 mg/L.[119,120] This antibiotic binds to peptidoglycan precursors in a similar manner as the glycopeptides, and it appears to have an extra binding site to peptidoglycan. Furthermore, oritavancin inserts into the cell membrane, producing depolarization that is thought to increase its bactericidal activity.[121] Clinical trials testing oritavancin in skin and soft tissue infections indicate that the antibiotic is safe and fulfilled the noninferiority criteria against the comparators[122]; however, data for the use of oritavancin in other human infections and against VRE are limited to case reports. Telavancin appears to have limited activity against glycopeptide-resistant enterococci with minimal inhibitory concentration in 90% of isolates (MIC_{90}) for vancomycin-resistant *E. faecalis* and *E. faecium* between 4 mg/L and 16 mg/L and 2 mg/L and 16 mg/L, respectively (although the MICs are severalfold lower than MICs of vancomycin). Similarly, dalbavancin does not bind peptidoglycan precursors terminating with D-Ala-D-Lac (produced by enterococci bearing VanA) and has little activity against VRE (MIC 16–32 mg/L). These compounds may be useful in the treatment of skin and soft tissue infections in which vancomycin-susceptible enterococci play a role.

Daptomycin

Daptomycin is a lipopeptide antibiotic that was approved by the US Food and Drug Administration (FDA) in 2003 for the treatment of complicated skin and soft tissue infections including infections with vancomycin-susceptible *E. faecalis,* and it was granted an additional indication in 2006 for *S. aureus* (including methicillin-resistant *S. aureus*) bacteremia and right-sided endocarditis. Daptomycin is not approved by the FDA for the treatment of *E. faecium* (regardless of susceptibility) or for VRE infections. The molecular events involved in its antibacterial action have not yet been completely elucidated, and it is thought that daptomycin inserts into the bacterial cell membrane in a calcium-dependent manner with preferential binding to septal areas, producing alterations of membrane homeostasis and cell division. These effects eventually lead to bacterial cell death by an unknown mechanism. In vitro, daptomycin exhibits rapid concentration-dependent bactericidal killing of enterococci; in vivo, the area under the curve (free drug)/MIC ratio appears to be the best parameter that correlates with clinical success.[123] The activity of daptomycin in vivo appears to be affected by its high binding affinity to albumin (90%–94%), and the unbound fraction might be crucial in the treatment of endovascular enterococcal infections when bactericidal therapy is a requirement. This observation, plus higher MICs and breakpoints than for staphylococci, has led to the notion that higher doses (10–12 mg/kg) may be of clinical benefit (see Figs. 200.2 and 200.3) and is supported by in vitro studies showing that higher doses of daptomycin may decrease the emergence of resistance on therapy.[124] Two nonrandomized cohort studies, one a retrospective study of enterococcal bacteremia in patients in a Veterans Affairs (VA) hospital in the United States and the other a prospective observational cohort in Taiwan, assessed the clinical impact of high-dose daptomycin (defined as ≥10 mg/kg/day and ≥9 mg/kg/day, respectively) on VRE bloodstream infections.[125,126] Both studies favored the use of high-dose daptomycin, and in the VA study high-dose daptomycin was significantly

associated with both lower 30-day mortality (RR, 0.83) and microbiologic clearance (HR, 0.70).[125]

Combination therapies that include daptomycin have been used in recalcitrant enterococcal infections. One of the most promising strategies involves the use of daptomycin plus a β-lactam to take advantage of an in vitro phenomenon known as the seesaw effect. This refers to the observation that resistance to cationic antimicrobial peptides (such as daptomycin or human cathelicidin LL-37) results in increased sensitivity to β-lactam antibiotics (such as ampicillin, ceftaroline, or ertapenem). Although robust clinical data are lacking, combinations of daptomycin plus ampicillin or ceftaroline have been successfully used to treat recurrent deep-seated enterococcal infections that have failed daptomycin monotherapy.[127,128] A variety of other combination regimens have been reported for difficult VRE infections. For example, failure of daptomycin monotherapy in the treatment of *E. faecium* endocarditis was overcome by the use of a combination of daptomycin (8 mg/kg/day), high-dose ampicillin, and gentamicin.[129] Similarly, the combination of daptomycin, gentamicin, and rifampin successfully treated a case of prosthetic valve endocarditis caused by a vancomycin-resistant isolate of *E. faecium* that failed with linezolid,[130] and in vivo experiments have demonstrated that the renal toxicity of gentamicin appears to be attenuated by the concomitant use of daptomycin. An additional anecdotal successful combination used in the treatment of endocarditis caused by a multidrug-resistant (including HLR to aminoglycosides) *E. faecium* included the combination of daptomycin (6 mg/kg every 48 hours) and tigecycline.[131]

Enterococci resistant to daptomycin have been well documented (daptomycin MICs range from 6 to >32 mg/L), although they remain relatively rare. Daptomycin resistance emerging during prolonged therapy (average exposure to daptomycin of 18 days) has been documented in *E. faecalis, E. faecium,* and *E. durans* isolates, and a retrospective study at a large cancer hospital found that exposure to ≥13 days of daptomycin in the preceding 3 months most significantly correlated with subsequent isolation of daptomycin-resistant *E. faecium* from the blood (60% vs. 11%).[132] De novo resistance has also been observed in isolates without previous exposure to the antibiotic.[133] Data suggest that a pivotal event in the mechanism of daptomycin resistance in enterococci involves changes in genes predicted to orchestrate the bacterial cell envelope stress response (designated *liaFSR*) and encoding enzymes of phospholipid metabolism (e.g., cardiolipin synthase).[134] Moreover, mutations in *liaFSR* in daptomycin-susceptible enterococci have been shown to lead to in vitro daptomycin tolerance (loss of the bactericidal activity of the antibiotic), and these mutations are common in isolates with MICs near the breakpoint (3–4 mg/L).[135,136] A retrospective cohort of 62 patients with VRE bacteremia found that MICs of 3–4 mg/L were associated with microbiologic failure, although MICs were not predictive of microbiologic failure or all-cause mortality in other studies.[126,137,138] Thus daptomycin dose and combination therapy should be carefully considered in patients with isolates near the breakpoint.

Linezolid

The efficacy of linezolid against enterococci (including VRE) has been evaluated in several clinical trials and in a meta-analysis.[139] In the case of endocarditis, controversial reports can be found in the literature regarding the outcomes of these patients because the antibiotic has been used when other recommended options have failed or when resistance or allergies to approved agents have been documented. In an intention-to-treat analysis of 22 patients with VRE endocarditis treated with linezolid on a compassionate use basis, cure was achieved in only 10 (45%) patients. Conversely, linezolid was used as a single agent in the treatment of 5 patients with endocarditis caused by *E. faecalis* (3 were vancomycin resistant) and 4 patients with *E. faecium* (all vancomycin resistant). The overall cure or improvement rate was 78% (7 of 9 patients), with development of thrombocytopenia in 33% of patients.

The American Heart Association (AHA)/Infectious Diseases Society of America (IDSA) lists linezolid as one of the two drugs (the other being daptomycin) that can be used as first-line therapy for endocarditis caused by *E. faecium* resistant to β-lactams, glycopeptides, and aminoglycosides[140] (evidence is "expert opinion"). The question of which antibiotic, linezolid or daptomycin, should be the preferred agent for treatment of VRE bloodstream infection remains undecided. There was no difference between the two drugs in one meta-analysis,[141] whereas in two others linezolid had lower all-cause[142] and infection-related[143] mortality. Each of the analyses had substantial limitations including small sample sizes, heterogeneous outcomes, and a lack of patient-specific data. A subsequent study using a large retrospective cohort of 644 patients admitted to a VA hospital with VRE bacteremia and treated with either daptomycin or linezolid found that treatment with linezolid was associated with higher 30-day all-cause mortality and microbiologic failure rates.[144] Furthermore, analysis of a propensity-matched cohort of VA patients with endocarditis due to VRE showed that daptomycin was associated with lower mortality than linezolid.[145] We suggest that linezolid should be used with caution in the treatment of VRE enterococcal endocarditis and only when combinations of β-lactams and aminoglycosides, high-dose daptomycin, or daptomycin plus other agents cannot be used because of resistance, toxicity, or therapeutic failure. In patients allergic to β-lactams, desensitization should be considered in severe infections caused by *E. faecalis* (see Fig. 200.2). Linezolid has also been successfully used in the treatment of enterococcal meningitis caused by different species, but no clinical trials have been conducted because of the paucity of cases.

Linezolid resistance appears to be increasing, and horizontal spread of specific linezolid-resistant outbreak strains has been reported[146] including in patients without previous exposure to the antibiotic. Risk factors for the acquisition of nosocomial linezolid-resistant strains included peripheral vascular disease; receipt of a solid-organ transplant; total parenteral nutrition; and administration of piperacillin-tazobactam, or cefepime, or both. The common mechanism of resistance involves mutations in the central loop of domain V of the 23S rRNA. The mutation G2576T (*E. coli* 23S rRNA gene numbering) is commonly found in resistant strains, and other mutations (G2505A, G2512T, G2513T, C2610G) have been found in enterococci, mainly in vitro. The rRNA mutations appear to interfere with the oxazolidinone interaction with its target at the core of the ribosomal peptidyltransferase center. *E. faecalis* and *E. faecium* contain four and six copies of the rRNA operons, respectively, and the increase in MIC of linezolid has been associated with the number of mutated rRNA genes[147]; intracellular homologous recombination between mutated and wild-type alleles may play a role in increasing the number of copies with the mutation. Studies in the GI tract of gnotobiotic mice also indicate that the dose and duration of linezolid exposure directly influence the number of mutated rRNA genes. Nonmutational resistance to linezolid is mediated by the presence of a gene designated *cfr* (chloramphenicol-florfenicol resistance), which was originally described on a plasmid in an animal isolate of *Staphylococcus sciuri,* and encodes an enzyme capable of methylating position A2503 of the 23S rRNA of bacterial ribosomes. The presence of *cfr* conferring linezolid resistance in a clinical isolate of *E. faecalis* indicated some evidence of animal-to-human transmission.[148]

The new oxazolidinone tedizolid has better in vitro activity against *cfr*-positive isolates. A second gene conferring resistance to linezolid is *optrA,* which encodes a protein similar to the adenosine triphosphate (ATP)–binding subunit of ATP-binding cassette transporters and mediates resistance to oxazolidinones and phenicols through ribosomal protection (displacement of the antibiotic from the site of action).[149] In contrast to *cfr,* the presence of *optrA* was associated with a fourfold to eightfold increase in the tedizolid MIC, which could have a clinically significant impact on the use of this agent.[150]

Tigecycline

Tigecycline is approved by the FDA for the treatment of complicated skin and soft tissue infections and abdominal infections caused by susceptible organisms including vancomycin-susceptible *E. faecalis*. Animal models of peritonitis and endocarditis have documented the efficacy of tigecycline against enterococci, regardless of the presence of vancomycin or tetracycline resistance. It is thought that its prolonged half-life, postantibiotic effect, and homogeneous diffusion into the cardiac vegetation could enhance the in vivo activity of this compound against enterococci in valvular vegetations. However, no clinical data are available to support the use of tigecycline monotherapy in enterococcal endocarditis or any other endovascular infections, and concerns over the

use of tigecycline for the treatment of bloodstream infections have been raised because only low serum concentrations are achieved at the recommended dose. Tigecycline may have a role as a part of combination therapy, especially for *E. faecium,* as the MIC_{90} is 0.12 to 0.25 μg/mL and tends to be slightly lower than for *S. aureus* or *E. faecalis* as determined in broad antimicrobial susceptibility surveys.[151,152]

Emergence of resistance to tigecycline during therapy has been documented in an enterococcal isolate (*E. faecalis*) from the urine of a patient who was receiving treatment for a respiratory infection caused by *Stenotrophomonas maltophilia*.[153] Resistance to tigecycline has been associated with changes in the S10 ribosomal protein in the 30S ribosomal subunit that lies near the binding site of the drug; it is likely that mutations interfere with the ability of tigecycline to effectively bind the 16S rRNA target.[154] Nonetheless, in phase III trials of complicated skin and soft tissue and intraabdominal infections, tigecycline was noninferior to the comparators (vancomycin-aztreonam and imipenem-cilastatin, respectively) against vancomycin-susceptible *E. faecalis,* supporting the potential clinical usefulness of tigecycline against enterococci.[155] As mentioned earlier, tigecycline has been successfully used in combination with daptomycin in the treatment of at least three patients with endocarditis and one patient with meningitis unresponsive to other regimens.

Quinupristin-Dalfopristin

Q-D is a parenteral, semisynthetic antibiotic combination of streptogramin type A (dalfopristin) and type B (quinupristin) that was the first FDA-approved antibiotic for the treatment of VRE infections (this indication was subsequently withdrawn). Q-D is not generally active against *E. faecalis* because of the presence of an ATP-binding cassette (ABC) protein designated Lsa (similar to *optrA* [see "Linezolid"]).[156] Q-D has been evaluated in patients with severe vancomycin-resistant *E. faecium* infections in two prospective noncomparative, emergency use studies, with overall success rates (clinical and bacteriologic) of approximately 65%.[157] Q-D side effects such as phlebitis, myalgias/arthralgias, and metabolic abnormalities appear to be the most relevant problems with this antibiotic, which may lead to treatment interruptions. Successful treatment of patients with endocarditis caused by a vancomycin-resistant *E. faecium* with several combination therapies, in which one of the components was Q-D, has been documented and includes Q-D plus doxycycline and rifampin and Q-D plus high-dose ampicillin (32 g/day).[158] Q-D has also been used successfully in the treatment of enterococcal meningitis (using intravenous and intrathecal administration).

Nonsusceptibility to Q-D in enterococci is due to several mechanisms including (1) the macrolide-lincosamide-streptogramin B (MLS_B) type of resistance mediated by the *erm* genes (encoding a 23S rRNA methyltransferase) that appears to decrease the bactericidal activity of Q-D in vitro and in vivo and (2) the presence of the *vatD* and *vatE* genes, which encode acetyltransferases that inactivate streptogramin A. These genes are usually carried on plasmids and confer resistance to the related streptogramin, virginiamycin, which is an antibiotic previously used as a growth promoter in the veterinary industry.

Other Antienterococcal Antimicrobials

Quinolones (mainly ciprofloxacin and moxifloxacin) have been reported as part of combination therapy for treatment of enterococcal infections (see Fig. 200.2). However, the increased rates of resistance observed, the selection of resistant mutants during therapy, and the lack of effect in certain animal models make the quinolones less appealing for enterococcal infections, particularly as monotherapy. A potential role of quinolones may be as long-term suppressive therapy against fluoroquinolone-susceptible enterococci in endovascular infections in combination with amoxicillin. Tetracyclines (doxycycline and minocycline) also have been sporadically used in enterococcal infections either as monotherapy or in combination with other compounds when isolates are susceptible to these antibiotics.

Although resistance to chloramphenicol in enterococci mediated by the chloramphenicol acetyltransferase enzyme has been long documented, the prevalence among VRE isolates appears to be low, and hence chloramphenicol was used early on in the treatment of resistant enterococcal infections. In a case series of 51 patients with VRE bloodstream infections treated with chloramphenicol, 61.1% demonstrated a clinical response, and 79.1% exhibited microbiologic eradication with no serious side effects that could be definitely attributed to chloramphenicol.[159] Similarly, successful treatment of prosthetic valve endocarditis and meningitis with chloramphenicol plus minocycline and chloramphenicol monotherapy, respectively, has been reported.[160,161] However, blood levels of this antibiotic at doses generally used (100 mg/kg/day divided every 6 hours) may not be adequate, and treatment failures have occurred; hence chloramphenicol should be considered only as an alternative in certain clinical settings (when available), and close monitoring for hematologic toxicity is strongly recommended.

Antibiotics that concentrate in the urine such as β-lactams (very high concentrations of ampicillin may be obtained in urine) could be potentially useful for the treatment of enterococcal UTIs, even in cases of isolates with increased ampicillin MICs. Nitrofurantoin also achieves good levels in urine, and a randomized open-label trial comparing nitrofurantoin for 5 days versus trimethoprim-sulfamethoxazole for 3 days in the treatment of UTIs including those caused by enterococci indicated that nitrofurantoin was equivalent to the comparator drug.[162] Successful treatment of UTIs caused by vancomycin-resistant and ampicillin-resistant *E. faecium* with nitrofurantoin in an outbreak setting (100 mg every 6 hours) has also been documented.[163] Similarly, fosfomycin tromethamine has activity against enterococci and has an FDA indication for treatment of UTI caused by *E. faecalis*. Although clinical trials are lacking, in vitro activity against *E. faecium* isolates from UTIs (MIC_{90}, 64 mg/L) indicates that it would seem a reasonable option to consider in UTIs caused by *E. faecium* that are susceptible using the *E. faecalis* criteria.[110]

Intrathecal antibiotics have been used in the treatment of enterococcal meningitis, mostly combined with systemic therapy. The antibiotics used include vancomycin, teicoplanin, gentamicin, daptomycin, and Q-D. However, there are no clear clinical data that favor the use of intrathecal antibiotics over systemic compounds alone in the management of enterococcal meningitis, and this approach may be considered in cases with multiresistant organisms in which systemic therapy fails and removal of intrathecal catheters or shunts cannot be achieved (see Table 200.3).

STREPTOCOCCUS GALLOLYTICUS (BOVIS) GROUP

Streptococci belonging to the previously designated *Streptococcus bovis* group are organisms that have been considered opportunistic pathogens in humans. These organisms also react with Lancefield group D antisera but can be differentiated from the enterococci, as they are PYR negative and do not grow in the presence of 6.5% sodium chloride. Growth on trypticase soy plus 5% sheep's blood agar typically produces γ-hemolytic or α-hemolytic colonies (see Table 200.1). Genetic data have led to a taxonomic reclassification within the *S. bovis* group, which traditionally had been divided into three different biotypes based on the fermentation of mannitol and the presence of β-glucuronidase activity. The former *S. bovis* biotype I (the most commonly associated with endocarditis and bacteremia) has been designated *S. gallolyticus* subsp. *gallolyticus (S. gallolyticus)*, and biotype II/2 has been designated *S. gallolyticus* subsp. *pasteurianus (S. pasteurianus)*. The former biotype II/1 has been divided into two species, *S. infantarius* subsp. *infantarius (S. infantarius)* and *S. infantarius* subsp. *coli (S. lutiensis)*.[164,165] This change in nomenclature has generated some confusion among clinicians because the important association between bacteremia/endocarditis caused by the *S. gallolyticus* group of organisms and colonic malignancies may have been missed because of the lack of recognition of the new species names. The differentiation between these species can be difficult at times. Nucleic acid tests including sequencing of 16S ribosomal DNA or whole-genome sequencing will allow accurate identification to the subspecies level. MALDI-TOF mass spectrometry often provides rapid and reliable identification to the species level, which is sufficient to lead to further pursuit of endocarditis or colorectal malignancy, if clinically warranted.[166] Although a degree of strain variability exists, the *S. gallolyticus* group of organisms (particularly *S. gallolyticus* subsp. *gallolyticus*, formerly *S. bovis* biotype I) has been found to adhere in vitro to individual proteins

of the extracellular matrix such as collagen, fibronectin, and fibrin, which is thought to be important in the pathogenesis of endocarditis.[167]

The *S. gallolyticus* group of organisms is estimated to cause approximately 7% of all cases of endocarditis and approximately 20% of streptococcal endocarditis. Bacteremia and endocarditis caused by the *S. gallolyticus* group of organisms have been highly associated with the presence of colonic malignancy (particularly *S. gallolyticus* subsp. *gallolyticus,* although *S. gallolyticus* subsp. *pasteurianus* has been linked to malignancy in other locations in the GI tract)[168,169] and hepatobiliary disease, although the reason for this association remains obscure. In vitro models of *S. gallolyticus* subsp. *gallolyticus* infection have suggested that the ability to form biofilm on collagen-rich surfaces and translocate at the site of premalignant colonic lesions while evading immune activation may underlie the association with endocarditis and colonic malignancy.[170] Further studies of host-pathogen interaction suggest that *S. gallolyticus* induces expression of β-catenin, promoting cell proliferation and tumorigenesis in cultured human colon cancer cell lines.[171] This suggests that not only is *S. gallolyticus* associated with GI malignancy, but that it also may contribute to pathogenesis. In a study analyzing the clinical characteristics of 20 cases of endocarditis (excluding drug addicts) caused by the *S. gallolyticus* group over 13 years, the aortic valve was the most frequent valve affected. Simultaneous involvement of two cardiac valves, moderate-to-severe regurgitation, and embolic events were also commonly found. Colonic neoplasms were documented in 77% of patients.[172]

The AHA/IDSA guidelines for infectious endocarditis recommend the use of a β-lactam (ceftriaxone or penicillin G) plus an aminoglycoside (gentamicin) for 2 weeks or a β-lactam alone (in patients older than 65 years of age with concomitant impairment of renal function or eighth cranial nerve function) for 4 weeks for the treatment of native valve endocarditis caused by the *S. gallolyticus* group when MICs to penicillin are ≤0.12 mg/L. For isolates with MICs greater than 0.12 but less than or equal to 0.5 mg/L, the combination of the β-lactam (4 weeks) and aminoglycoside (2 weeks) should always be considered. Similar recommendations are given for the treatment of prosthetic valve endocarditis, although the duration of β-lactam therapy should be extended to 6 weeks.[140] For isolates with MIC greater than 0.5 mg/L, 4 to 6 weeks of therapy with ampicillin or penicillin G plus gentamicin is recommended. Vancomycin should be used in patients unable to tolerate the β-lactams, and a minimum of 4 or 6 weeks of therapy is recommended for native or prosthetic valves, respectively. The *vanB* gene cluster conferring high-level vancomycin resistance has been identified in members of the *S. gallolyticus* group. Shorter regimens should be considered for bacteremia without endocarditis, and patients should undergo evaluation of the GI tract to rule out malignancies, particularly if *S. gallolyticus* is involved.

LEUCONOSTOC SPECIES

Members of the *Leuconostoc* genus are catalase-negative, gram-positive cocci usually arranged in pairs or chains and often found in plants, dairy products, and foods. A minority (up to 31%) of *Leuconostoc* spp. react with group D antisera, and they do not produce either PYR or leucine aminopeptidase.[173] Also, in contrast to the enterococci and *S. gallolyticus* group, *Leuconostoc* spp. are capable of producing gas on fermentation of glucose. Strains exhibit variable growth in broth containing 6.5% sodium chloride, at 10°C, and at 45°C (see Table 200.1). Although these organisms were previously considered of low pathogenic potential for humans, they have emerged as sporadic causes of infection. Because *Leuconostoc* spp. can phenotypically resemble *Streptococcus, Enterococcus, Pediococcus,* and *Lactococcus,* they may sometimes be misidentified; their distinguishing characteristics include vancomycin resistance, negative reaction for PYR and leucine aminopeptidase (see Table 200.1), and lack of gas production from glucose. The most common *Leuconostoc* spp. isolated from human infections are *L. mesenteroides, L. pseudomesenteroides, L. paramesenteroides, L. citreum,* and *L. lactis.* A taxonomic study using 16S rRNA sequences indicated that members of the *Leuconostoc* genus could be grouped into three subclusters: *L. mesenteroides* subcluster, which contains most of the human pathogenic species; *L. fructosum* subcluster, which was proposed to be renamed as *Fructobacillus;* and *L. fallax* subcluster.[174]

Leuconostoc spp. appear to be normal colonizers of the GI tract, which could be the initial portal of entry in human infections. The first report of human infections with *Leuconostoc* spp. was in 1985 in two immunocompromised patients with bloodstream infections,[175] and since then they have been implicated in a variety of infection such as bacteremia (including catheter-related infections), endocarditis, pulmonary infections, meningitis, brain and liver abscesses, and osteomyelitis, among others, affecting both immunocompetent and immunocompromised patients (majority) including children and newborns. It has been postulated that previous antibiotic therapy (e.g., vancomycin), presence of intravascular devices, and underlying GI disease may be risk factors for *Leuconostoc* infections. Nosocomial outbreaks of *Leuconostoc* spp. have also been described, suggesting that they have the potential to disseminate in the hospital environment.

Antimicrobial susceptibility testing is crucial for treatment of *Leuconostoc* infections because these bacteria are naturally resistant to glycopeptides owing to the production of peptidoglycan precursors ending in D-alanine-D-lactate. The organisms are usually susceptible to penicillin G and ampicillin (although MICs tend to be higher than streptococci), which are generally more active than the cephalosporins and should be considered as the treatment of choice. The carbapenems (i.e., imipenem) have good activity, but a carbapenem-resistant isolate from a patient with postoperative meningitis has been documented. Resistance to trimethoprim, sulfonamide, and fosfomycin appears to be common among the members of the *Leuconostoc* genus. Erythromycin, clindamycin, tetracycline, minocycline, and chloramphenicol appear to remain active against the majority of the clinical isolates. Linezolid MICs are higher for *Leuconostoc* spp. compared with streptococci (MIC_{90} of 4 mg/L), whereas daptomycin is highly active in vitro and has been used successfully in the treatment of catheter-related bacteremia caused by *Leuconostoc* spp. for two patients who underwent bone marrow transplantation.[176]

Key References

The complete reference list is available online at Expert Consult.

1. Thiercelin E. Sur un diplocoque saphrophyte de l'intestin susceptible de devenir pathogene. *C R Soc Biol.* 1899;5:269–271.
2. MacCallum WG, Hastings TW. A case of acute endocarditis caused by *Micrococcus zymogenes* (nov. spec.), with a description of the microorganism. *J Exp Med.* 1899;4:521–534.
3. Andrews F, Horder T. A study of streptococci pathogenic for man. *Lancet.* 1906;2:708–713.
7. Murray BE. The life and times of the *Enterococcus*. *Clin Microbiol Rev.* 1990;3:46–65.
8. Kalina A. The taxonomy and nomenclature of enterococci. *Int J Syst Bacteriol.* 1970;20:185–189.
10. Lebreton F, Manson AL, Saavedra JT, et al. Tracing the enterococci from Paleozoic origins to the hospital. *Cell.* 2017;169:849–861.
12. Dutka-Malen S, Evers S, Courvalin P. Detection of glycopeptide resistance genotypes and identification to the species level of clinically relevant enterococci by PCR. *J Clin Microbiol.* 1995;33:24–27.
15. Donskey CJ, Hanrahan JA, Hutton RA, et al. Effect of parenteral antibiotic administration on the establishment of colonization with vancomycin-resistant *Enterococcus faecium* in the mouse gastrointestinal tract. *J Infect Dis.* 2000;181:1830–1833.
18. Brandl K, Plitas G, Mihu CN, et al. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. *Nature.* 2008;455:804–807.
19. Ubeda C, Taur Y, Jenq RR, et al. Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J Clin Invest.* 2010;120:4332–4341.
21. Caballero S, Kim S, Carter RA, et al. Cooperating commensals restore colonization resistance to vancomycin-resistant *Enterococcus faecium*. *Cell Host Microbe.* 2017;21:592–602.
23. Gilmore MS, Segarra RA, Booth MC, et al. Genetic structure of the *Enterococcus faecalis* plasmid pAD1-encoded cytolytic toxin system and its relationship to antibiotic determinants. *J Bacteriol.* 1994;176:7335–7344.
24. Singh KV, Qin X, Weinstock GM, et al. Generation and testing of mutants of *Enterococcus faecalis* in a mouse peritonitis model. *J Infect Dis.* 1998;178:1416–1420.
29. Choudhury T, Singh KV, Sillanpaa J, et al. Importance of two *Enterococcus faecium* loci encoding Gls-like proteins for in vitro bile salts stress response and virulence. *J Infect Dis.* 2011;203:1147–1154.
32. Zhang X, Top J, de Been M, et al. Identification of a genetic determinant in clinical *Enterococcus faecium* strains that contributes to intestinal colonization during antibiotic treatment. *J Infect Dis.* 2013;207:1780–1786.
36. Liu Q, Ponnuraj K, Xu Y, et al. The *Enterococcus faecalis* MSCRAMM ACE binds its ligand by the Collagen Hug model. *J Biol Chem.* 2007;282:19629–19637.
39. Nallapareddy SR, Singh KV, Sillanpaa J, et al. Endocarditis and biofilm-associated pili of *Enterococcus faecalis*. *J Clin Invest.* 2006;116:2799–2807.

47. Hancock LE, Gilmore MS. The capsular polysaccharide of *Enterococcus faecalis* and its relationship to other polysaccharides in the cell wall. *Proc Natl Acad Sci USA*. 2002;99:1574–1579.
48. Theilacker C, Kropec A, Hammer F, et al. Protection against *Staphylococcus aureus* by antibody to the polyglycerolphosphate backbone of heterologous lipoteichoic acid. *J Infect Dis*. 2012;205:1076–1085.
49. Arias CA, Panesso D, Singh KV, et al. Cotransfer of antibiotic resistance genes and a hyl_{Efm}-containing virulence plasmid in *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2009;53:4240–4246.
50. Rice LB, Carias L, Rudin S, et al. A potential virulence gene, hyl_{Efm}, predominates in *Enterococcus faecium* of clinical origin. *J Infect Dis*. 2003;187:508–512.
51. Lebreton F, van Schaik W, Sanguinetti M, et al. AsrR is an oxidative stress sensing regulator modulating *Enterococcus faecium* opportunistic traits, antimicrobial resistance, and pathogenicity. *PLoS Pathog*. 2012;8:e1002834.
52. Shankar N, Baghdayan AS, Gilmore MS. Modulation of virulence within a pathogenicity island in vancomycin-resistant *Enterococcus faecalis*. *Nature*. 2002;417:746–750.
53. Paulsen IT, Banerjei L, Myers GS, et al. Role of mobile DNA in the evolution of vancomycin-resistant *Enterococcus faecalis*. *Science*. 2003;299:2071–2074.
54. Palmer KL, Gilmore MS. Multidrug-resistant enterococci lack CRISPR-cas. *MBio*. 2010;1:pii:e00227-10.
56. Lebreton F, van Schaik W, McGuire AM, et al. Emergence of epidemic multidrug-resistant *Enterococcus faecium* from animal and commensal strains. *MBio*. 2013;4:pii: e00534-13.
57. Galloway-Pena J, Roh JH, Latorre M, et al. Genomic and SNP analyses demonstrate a distant separation of the hospital and community-associated clades of *Enterococcus faecium*. *PLoS ONE*. 2012;7:e30187.
58. Palmer KL, Godfrey P, Griggs A, et al. Comparative genomics of enterococci: variation in *Enterococcus faecalis*, clade structure in *E. faecium*, and defining characteristics of *E. gallinarum* and *E. casseliflavus*. *MBio*. 2012;3:e00318–11.
60. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
62. Vergis EN, Hayden MK, Chow JW, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. A prospective multicenter study. *Ann Intern Med*. 2001;135:484–492.
63. Furtado GH, Mendes RE, Pignatari AC, et al. Risk factors for vancomycin-resistant *Enterococcus faecalis* bacteremia in hospitalized patients: an analysis of two case-control studies. *Am J Infect Control*. 2006;34:447–451.
64. LeDell K, Muto CA, Jarvis WR, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Control Hosp Epidemiol*. 2003;24:639–641.
67. Olivier CN, Blake RK, Steed LL, et al. Risk of vancomycin-resistant *Enterococcus* (VRE) bloodstream infection among patients colonized with VRE. *Infect Control Hosp Epidemiol*. 2008;29:404–409.
69. Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. *Infect Control Hosp Epidemiol*. 2003;24:690–698.
80. Fernandez Guerrero ML, Goyenechea A, Verdejo C, et al. Enterococcal endocarditis on native and prosthetic valves: a review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. *Medicine (Baltimore)*. 2007;86:363–377.
89. Pintado V, Cabellos C, Moreno S, et al. Enterococcal meningitis: a clinical study of 39 cases and review of the literature. *Medicine (Baltimore)*. 2003;82:346–364.
92. Gorbach SL. Intraabdominal infections. *Clin Infect Dis*. 1993;17:961–965.
94. Burnett RJ, Haverstock DC, Dellinger EP, et al. Definition of the role of enterococcus in intraabdominal infection: analysis of a prospective randomized trial. *Surgery*. 1995;118:716–721, discussion 721–723.
101. Chang S, Sievert DM, Hageman JC, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. *N Engl J Med*. 2003;348:1342–1347.
104. Murray BE. Vancomycin-resistant enterococcal infections. *N Engl J Med*. 2000;342:710–721.
107. Montealegre MC, Roh JH, Rae M, et al. Differential penicillin-binding protein 5 (PBP5) levels in the *Enterococcus faecium* clades with different levels of ampicillin resistance. *Antimicrob Agents Chemother*. 2016;61:e02034–16.
112. Mederski-Samoraj BD, Murray BE. High-level resistance to gentamicin in clinical isolates of enterococci. *J Infect Dis*. 1983;147:751–757.
115. Gavalda J, Len O, Miro JM, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. *Ann Intern Med*. 2007;146:574–579.
116. Fernandez-Hidalgo N, Almirante B, Gavalda J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *Enterococcus faecalis* infective endocarditis. *Clin Infect Dis*. 2013;56:1261–1268.
122. Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. *N Engl J Med*. 2014;370:2180–2190.
125. Britt NS, Potter EM, Patel N, et al. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of vancomycin-resistant enterococcal bacteremia among Veterans Affairs patients. *Clin Infect Dis*. 2017;64:605–613.
126. Chuang YC, Lin HY, Chen PY, et al. Effect of daptomycin dose on the outcome of vancomycin-resistant, daptomycin-susceptible *Enterococcus faecium* bacteremia. *Clin Infect Dis*. 2017;64:1026–1034.
127. Sakoulas G, Bayer AS, Pogliano J, et al. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2012;56:838–844.
128. Sakoulas G, Rose W, Nonejuie P, et al. Ceftaroline restores daptomycin activity against daptomycin-nonsusceptible vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2014;58:1494–1500.
134. Arias CA, Panesso D, McGrath DM, et al. Genetic basis for in vivo daptomycin resistance in enterococci. *N Engl J Med*. 2011;365:892–900.
137. Shukla BS, Shelburne S, Reyes K, et al. Influence of minimum inhibitory concentration in clinical outcomes of *Enterococcus faecium* bacteremia treated with daptomycin: is it time to change the breakpoint? *Clin Infect Dis*. 2016;62:1514–1520.
146. Herrero IA, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant *Enterococcus faecium*. *N Engl J Med*. 2002;346:867–869.
148. Diaz L, Kiratisin P, Mendes RE, et al. Transferable plasmid-mediated resistance to linezolid due to *cfr* in a human clinical isolate of *Enterococcus faecalis*. *Antimicrob Agents Chemother*. 2012;56:3917–3922.
164. Schlegel L, Grimont F, Ageron E, et al. Reappraisal of the taxonomy of the *Streptococcus bovis/Streptococcus equinus* complex and related species: description of *Streptococcus gallolyticus* subsp. *gallolyticus* subsp. nov., *S. gallolyticus* subsp. *macedonicus* subsp. nov. and *S. gallolyticus* subsp. *pasteurianus* subsp. nov. *Int J Syst Evol Microbiol*. 2003;53:631–645.
165. Boleij A, van Gelder MM, Swinkels DW, et al. Clinical importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: systematic review and meta-analysis. *Clin Infect Dis*. 2011;53: 870–878.
174. Endo A, Okada S. Reclassification of the genus *Leuconostoc* and proposals of *Fructobacillus fructosus* gen. nov., comb. nov., *Fructobacillus durionis* comb. nov., *Fructobacillus ficulneus* comb. nov. and *Fructobacillus pseudoficulneus* comb. nov. *Int J Syst Evol Microbiol*. 2008;58:2195–2205.

References

1. Thiercelin E. Sur un diplocoque saphrophyte de l'intestin susceptible de devenir pathogene. *C R Soc Biol*. 1899;5:269–271.
2. MacCallum WG, Hastings TW. A case of acute endocarditis caused by *Micrococcus zymogenes* (nov. spec.), with a description of the microorganism. *J Exp Med*. 1899;4:521–534.
3. Andrews F, Horder T. A study of streptococci pathogenic for man. *Lancet*. 1906;2:708–713.
4. Sherman JM. The streptococci. *Bacteriol Rev*. 1937;1: 3–97.
5. Orla-Jensen S. The lactic acid bacteria. *Mem Acad Royal Sci Danemark Sect Sci Ser*. 1919;5:81–197.
6. Barnes EM. Tetrazolium reduction as a means of differentiating *Streptococcus faecalis* from *Streptococcus faecium*. *J Gen Microbiol*. 1956;14:57–68.
7. Murray BE. The life and times of the *Enterococcus*. *Clin Microbiol Rev*. 1990;3:46–65.
8. Kalina A. The taxonomy and nomenclature of enterococci. *Int J Syst Bacteriol*. 1970;20:185–189.
9. Schleifer KH, Kilpper-Balz R. Transfer of *Streptococcus faecalis* and *Streptococcus faecium* to the genus *Enterococcus* nom. rev. as *Enterococcus faecalis* comb. nov. and *Enterococcus faecium* comb. nov. *Int J Syst Bacteriol*. 1984;34:31–34.
10. Lebreton F, Manson AL, Saavedra JT, et al. Tracing the enterococci from Paleozoic origins to the hospital. *Cell*. 2017;169:849–861.
11. Ford M, Perry JD, Gould FK. Use of cephalexin-aztreonam-arabinose agar for selective isolation of *Enterococcus faecium*. *J Clin Microbiol*. 1994;32: 2999–3001.
12. Dutka-Malen S, Evers S, Courvalin P. Detection of glycopeptide resistance genotypes and identification to the species level of clinically relevant enterococci by PCR. *J Clin Microbiol*. 1995;33:24–27.
13. Duh RW, Singh KV, Malathum K, et al. In vitro activity of 19 antimicrobial agents against enterococci from healthy subjects and hospitalized patients and use of an *ace* gene probe from *Enterococcus faecalis* for species identification. *Microb Drug Resist*. 2001;7:39–46.
14. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. 2006;124:837–848.
15. Donskey CJ, Hanrahan JA, Hutton RA, et al. Effect of parenteral antibiotic administration on the establishment of colonization with vancomycin-resistant *Enterococcus faecium* in the mouse gastrointestinal tract. *J Infect Dis*. 2000;181:1830–1833.
16. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. *Lancet Infect Dis*. 2001;1:101–114.
17. Stiefel U, Pultz NJ, Helfand MS, et al. Increased susceptibility to vancomycin-resistant *Enterococcus* intestinal colonization persists after completion of anti-anaerobic antibiotic treatment in mice. *Infect Control Hosp Epidemiol*. 2004;25:373–379.
18. Brandl K, Plitas G, Mihu CN, et al. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. *Nature*. 2008;455:804–807.
19. Ubeda C, Taur Y, Jenq RR, et al. Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J Clin Invest*. 2010;120:4332–4341.
20. Ubeda C, Bucci V, Caballero S, et al. Intestinal microbiota containing *Barnesiella* species cures vancomycin-resistant *Enterococcus faecium* colonization. *Infect Immun*. 2013;81:965–973.
21. Caballero S, Kim S, Carter RA, et al. Cooperating commensals restore colonization resistance to vancomycin-resistant *Enterococcus faecium*. *Cell Host Microbe*. 2017;21:592–602.
22. Stiefel U, Rao A, Pultz MJ, et al. Suppression of gastric acid production by proton pump inhibitor treatment facilitates colonization of the large intestine by vancomycin-resistant *Enterococcus* spp. and *Klebsiella pneumoniae* in clindamycin-treated mice. *Antimicrob Agents Chemother*. 2006;50:3905–3907.
23. Gilmore MS, Segarra RA, Booth MC, et al. Genetic structure of the *Enterococcus faecalis* plasmid pAD1-encoded cytolytic toxin system and its relationship to antibiotic determinants. *J Bacteriol*. 1994;176: 7335–7344.
24. Singh KV, Qin X, Weinstock GM, et al. Generation and testing of mutants of *Enterococcus faecalis* in a mouse peritonitis model. *J Infect Dis*. 1998;178:1416–1420.
25. Thomas VC, Thurlow LR, Boyle D, et al. Regulation of autolysis-dependent extracellular DNA release by *Enterococcus faecalis* extracellular proteases influences biofilm development. *J Bacteriol*. 2008;190:5690–5698.
26. Qin X, Singh KV, Weinstock GM, et al. Characterization of *fsr*, a regulator controlling expression of gelatinase and serine protease in *Enterococcus faecalis* OG1RF. *J Bacteriol*. 2001;183:3372–3382.
27. Bourgogne A, Hilsenbeck SG, Dunny GM, et al. Comparison of OG1RF and an isogenic *fsrB* deletion mutant by transcriptional analysis: the Fsr system of *Enterococcus faecalis* is more than the activator of gelatinase and serine protease. *J Bacteriol*. 2006;188:2875–2884.
28. Teng F, Nannini EC, Murray BE. Importance of *gls24* in virulence and stress response of *Enterococcus faecalis* and use of the Gls24 protein as a possible immunotherapy target. *J Infect Dis*. 2005;191:472–480.
29. Choudhury T, Singh KV, Sillanpaa J, et al. Importance of two *Enterococcus faecium* loci encoding Gls-like proteins for in vitro bile salts stress response and virulence. *J Infect Dis*. 2011;203:1147–1154.
30. Nannini EC, Teng F, Singh KV, et al. Decreased virulence of a *gls24* mutant of *Enterococcus faecalis* OG1RF in an experimental endocarditis model. *Infect Immun*. 2005;73:7772–7774.
31. Müller M, Reiß S, Schlüter R, et al. Deletion of membrane-associated Asp23 leads to upregulation of cell wall stress genes in *Staphylococcus aureus*. *Mol Microbiol*. 2014;93:1259–1268.
32. Zhang X, Top J, de Been M, et al. Identification of a genetic determinant in clinical *Enterococcus faecium* strains that contributes to intestinal colonization during antibiotic treatment. *J Infect Dis*. 2013;207:1780–1786.
33. Paganelli FL, Huebner J, Singh KV, et al. Genome-wide screening identifies phosphotransferase system permease BepA to be involved in *Enterococcus faecium* endocarditis and biofilm formation. *J Infect Dis*. 2016;214:189–195.
34. Rozdzinski E, Marre R, Susa M, et al. Aggregation substance-mediated adherence of *Enterococcus faecalis* to immobilized extracellular matrix proteins. *Microb Pathog*. 2001;30:211–220.
35. Tendolkar PM, Baghdayan AS, Shankar N. The N-terminal domain of enterococcal surface protein, Esp, is sufficient for Esp-mediated biofilm enhancement in *Enterococcus faecalis*. *J Bacteriol*. 2005;187:6213–6222.
36. Liu Q, Ponnuraj K, Xu Y, et al. The *Enterococcus faecalis* MSCRAMM ACE binds its ligand by the Collagen Hug model. *J Biol Chem*. 2007;282:19629–19637.
37. Nallapareddy SR, Singh KV, Okhuysen PC, et al. A functional collagen adhesin gene, acm, in clinical isolates of *Enterococcus faecium* correlates with the recent success of this emerging nosocomial pathogen. *Infect Immun*. 2008;76:4110–4119.
38. Brinster S, Posteraro B, Bierne H, et al. Enterococcal leucine-rich repeat-containing protein involved in virulence and host inflammatory response. *Infect Immun*. 2007;75:4463–4471.
39. Nallapareddy SR, Singh KV, Sillanpaa J, et al. Endocarditis and biofilm-associated pili of *Enterococcus faecalis*. *J Clin Invest*. 2006;116:2799–2807.
40. Singh KV, Nallapareddy SR, Murray BE. Importance of the *ebp* (endocarditis- and biofilm-associated pilus) locus in the pathogenesis of *Enterococcus faecalis* ascending urinary tract infection. *J Infect Dis*. 2007;195:1671–1677.
41. Hendrickx AP, Bonten MJ, van Luit-Asbroek M, et al. Expression of two distinct types of pili by a hospital-acquired *Enterococcus faecium* isolate. *Microbiology*. 2008;154:3212–3223.
42. Arduino RC, Jacques-Palaz K, Murray BE, et al. Resistance of *Enterococcus faecium* to neutrophil-mediated phagocytosis. *Infect Immun*. 1994;62: 5587–5594.
43. Huebner J, Quaas A, Krueger WA, et al. Prophylactic and therapeutic efficacy of antibodies to a capsular polysaccharide shared among vancomycin-sensitive and -resistant enterococci. *Infect Immun*. 2000;68:4631–4636.
44. Huebner J, Wang Y, Krueger WA, et al. Isolation and chemical characterization of a capsular polysaccharide antigen shared by clinical isolates of *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium*. *Infect Immun*. 1999;67:1213–1219.
45. Maekawa S, Yoshioka M, Kumamoto Y. Proposal of a new scheme for the serological typing of *Enterococcus faecalis* strains. *Microbiol Immunol*. 1992;36:671–681.
46. Teng F, Jacques-Palaz KD, Weinstock GM, et al. Evidence that the enterococcal polysaccharide antigen gene (epa) cluster is widespread in *Enterococcus faecalis* and influences resistance to phagocytic killing of *E. faecalis*. *Infect Immun*. 2002;70:2010–2015.
47. Hancock LE, Gilmore MS. The capsular polysaccharide of *Enterococcus faecalis* and its relationship to other polysaccharides in the cell wall. *Proc Natl Acad Sci USA*. 2002;99:1574–1579.
48. Theilacker C, Kropec A, Hammer F, et al. Protection against *Staphylococcus aureus* by antibody to the polyglycerolphosphate backbone of heterologous lipoteichoic acid. *J Infect Dis*. 2012;205:1076–1085.
49. Arias CA, Panesso D, Singh KV, et al. Cotransfer of antibiotic resistance genes and a *hylEfm*-containing virulence plasmid in *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2009;53:4240–4246.
50. Rice LB, Carias L, Rudin S, et al. A potential virulence gene, *hylEfm*, predominates in *Enterococcus faecium* of clinical origin. *J Infect Dis*. 2003;187:508–512.
51. Lebreton F, van Schaik W, Sanguinetti M, et al. AsrR is an oxidative stress sensing regulator modulating *Enterococcus faecium* opportunistic traits, antimicrobial resistance, and pathogenicity. *PLoS Pathog*. 2012;8: e1002834.
52. Shankar N, Baghdayan AS, Gilmore MS. Modulation of virulence within a pathogenicity island in vancomycin-resistant *Enterococcus faecalis*. *Nature*. 2002;417:746–750.
53. Paulsen IT, Banerjei L, Myers GS, et al. Role of mobile DNA in the evolution of vancomycin-resistant *Enterococcus faecalis*. *Science*. 2003;299:2071–2074.
54. Palmer KL, Gilmore MS. Multidrug-resistant enterococci lack CRISPR-cas. *MBio*. 2010;1:pii:e00227-10.
55. Bourgogne A, Garsin DA, Qin X, et al. Large scale variation in *Enterococcus faecalis* illustrated by the genome analysis of strain OG1RF. *Genome Biol*. 2008;9:R110.
56. Lebreton F, van Schaik W, McGuire AM, et al. Emergence of epidemic multidrug-resistant *Enterococcus faecium* from animal and commensal strains. *MBio*. 2013;4:pii: e00534-13.
57. Galloway-Pena J, Roh JH, Latorre M, et al. Genomic and SNP analyses demonstrate a distant separation of the hospital and community-associated clades of *Enterococcus faecium*. *PLoS ONE*. 2012;7:e30187.
58. Palmer KL, Godfrey P, Griggs A, et al. Comparative genomics of enterococci: variation in *Enterococcus faecalis*, clade structure in *E. faecium*, and defining characteristics of *E. gallinarum* and *E. casseliflavus*. *MBio*. 2012;3:e00318–11.
59. Contreras GA, DiazGranados CA, Cortes L, et al. Nosocomial outbreak of *Enteroccocus gallinarum*: untaming of rare species of enterococci. *J Hosp Infect*. 2008;70:346–352.
60. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
61. Goodman ER, Platt R, Bass R, et al. Impact of an environmental cleaning intervention on the presence of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci on surfaces in intensive care unit rooms. *Infect Control Hosp Epidemiol*. 2008;29:593–599.
62. Vergis EN, Hayden MK, Chow JW, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. A prospective multicenter study. *Ann Intern Med*. 2001;135:484–492.
63. Furtado GH, Mendes RE, Pignatari AC, et al. Risk factors for vancomycin-resistant *Enterococcus faecalis* bacteremia in hospitalized patients: an analysis of two case-control studies. *Am J Infect Control*. 2006;34:447–451.
64. LeDell K, Muto CA, Jarvis WR, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Control Hosp Epidemiol*. 2003;24:639–641.
65. Snyder GM, Thom KA, Furuno JP, et al. Detection of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci on the gowns and gloves of healthcare workers. *Infect Control Hosp Epidemiol*. 2008;29:583–589.
66. Weinstock DM, Conlon M, Iovino C, et al. Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2007;13:615–621.
67. Olivier CN, Blake RK, Steed LL, et al. Risk of vancomycin-resistant *Enterococcus* (VRE) bloodstream infection among patients colonized with VRE. *Infect Control Hosp Epidemiol*. 2008;29:404–409.
68. Roghmann MC, McCarter RJ Jr, Brewrink J, et al. *Clostridium difficile* infection is a risk factor for bacteremia due to vancomycin-resistant enterococci (VRE) in VRE-colonized patients with acute leukemia. *Clin Infect Dis*. 1997;25:1056–1059.
69. Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. *Infect Control Hosp Epidemiol*. 2003;24:690–698.
70. DiazGranados CA, Zimmer SM, Klein M, et al. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal

bloodstream infections: a meta-analysis. *Clin Infect Dis*. 2005;41:327–333.

71. Prematunge C, MacDougall C, Johnstone J, et al. VRE and VSE bacteremia outcomes in the era of effective VRE therapy: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2016;37:26–35.
72. Garrison RN, Fry DE, Berberich S, et al. Enterococcal bacteremia: clinical implications and determinants of death. *Ann Surg*. 1982;196:43–47.
73. Lagnf AM, Zasowski EJ, Claeys KC, et al. Comparison of clinical outcomes and risk factors in polymicrobial versus monomicrobial enterococcal bloodstream infections. *Am J Infect Control*. 2016;44:917–921.
74. Ghanem G, Hachem R, Jiang Y, et al. Outcomes for and risk factors associated with vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* bacteremia in cancer patients. *Infect Control Hosp Epidemiol*. 2007;28:1054–1059.
75. Zeana C, Kubin CJ, Della-Latta P, et al. Vancomycin-resistant *Enterococcus faecium* meningitis successfully managed with linezolid: case report and review of the literature. *Clin Infect Dis*. 2001;33:477–482.
76. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169:463–473.
77. Dahl A, Lauridsen TK, Arpi M, et al. Risk factors of endocarditis in patients with *Enterococcus faecalis* bacteremia: external validation of the NOVA score. *Clin Infect Dis*. 2016;63:771–775.
78. Bouza E, Kestler M, Beca T, et al. The NOVA score: a proposal to reduce the need for transesophageal echocardiography in patients with enterococcal bacteremia. *Clin Infect Dis*. 2015;60:528–535.
79. Rice LB, Calderwood SB, Eliopoulos GM, et al. Enterococcal endocarditis: a comparison of prosthetic and native valve disease. *Rev Infect Dis*. 1991;13:1–7.
80. Fernandez Guerrero ML, Goyenechea A, Verdejo C, et al. Enterococcal endocarditis on native and prosthetic valves: a review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. *Medicine (Baltimore)*. 2007;86:363–377.
81. Pericàs JM, Corredoira J, Moreno A, et al. Relationship between *Enterococcus faecalis* infective endocarditis and colorectal neoplasm: preliminary results from a cohort of 154 patients. *Rev Esp Cardiol (Engl Ed)*. 2017;70:451–458.
82. Bayer AS, Brenner RJ, Galpin JE, et al. Severe disabling polyarthritis associated with bacterial endocarditis. *West J Med*. 1975;123:404–406.
83. Mulleman D, Philippe P, Senneville E, et al. Streptococcal and enterococcal spondylodiscitis (vertebral osteomyelitis). High incidence of infective endocarditis in 50 cases. *J Rheumatol*. 2006;33:91–97.
84. Johnson JD, Raff MJ, Barnwell PA, et al. Splenic abscess complicating infectious endocarditis. *Arch Intern Med*. 1983;143:906–912.
85. MacEachern P, Giannoccaro JP, Elsayed S, et al. A rare case of pleuropulmonary infection and septic shock associated with *Enterococcus faecium* endocarditis. *J Infect*. 2005;50:84–88.
86. Anderson DJ, Olaison L, McDonald JR, et al. Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the International Collaboration on Endocarditis-merged database. *Eur J Clin Microbiol Infect Dis*. 2005;24:665–670.
87. Chirouze C, Athan E, Alla F, et al. Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. *Clin Microbiol Infect*. 2013;19:1140–1147.
88. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med*. 1993;328:21–28.
89. Pintado V, Cabellos C, Moreno S, et al. Enterococcal meningitis: a clinical study of 39 cases and review of the literature. *Medicine (Baltimore)*. 2003;82:346–364.
90. Nagai K, Yuge K, Ono E, et al. *Enterococcus faecium* meningitis in a child. *Pediatr Infect Dis J*. 1994;13:1016–1017.
91. Harbarth S, Uckay I. Are there patients with peritonitis who require empiric therapy for enterococcus? *Eur J Clin Microbiol Infect Dis*. 2004;23:73–77.
92. Gorbach SL. Intraabdominal infections. *Clin Infect Dis*. 1993;17:961–965.
93. Onderdonk AB, Bartlett JG, Louie T, et al. Microbial synergy in experimental intra-abdominal abscess. *Infect Immun*. 1976;13:22–26.
94. Burnett RJ, Haverstock DC, Dellinger EP, et al. Definition of the role of enterococcus in intraabdominal infection: analysis of a prospective randomized trial. *Surgery*. 1995;118:716–721, discussion 721–723.
95. Clock SA, Jia H, Patel S, et al. Infant colonization with methicillin-resistant Staphylococcus aureus or vancomycin-resistant enterococci preceding neonatal intensive care unit discharge. *J Pediatric Infect Dis Soc*. 2017;6:e144–e148.
96. Graham PL 3rd. Staphylococcal and enterococcal infections in the neonatal intensive care unit. *Semin Perinatol*. 2002;26:322–331.
97. Garges HP, Moody MA, Cotten CM, et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? *Pediatrics*. 2006;117:1094–1100.
98. Coudron PE, Mayhall CG, Facklam RR, et al. *Streptococcus faecium* outbreak in a neonatal intensive care unit. *J Clin Microbiol*. 1984;20:1044–1048.
99. Luginbuhl LM, Rotbart HA, Facklam RR, et al. Neonatal enterococcal sepsis: case-control study and description of an outbreak. *Pediatr Infect Dis J*. 1987;6:1022–1026.
100. Till M, Wixson RL, Pertel PE. Linezolid treatment for osteomyelitis due to vancomycin-resistant *Enterococcus faecium*. *Clin Infect Dis*. 2002;34:1412–1414.
101. Chang S, Sievert DM, Hageman JC, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. *N Engl J Med*. 2003;348:1342–1347.
102. Pehlivan Y, Toy MA, Karaoglan I, et al. *Enterococcus avium* cerebral abscess. *Intern Med*. 2007;46:1280.
103. Krogstad DJ, Pargwette AR. Defective killing of enterococci: a common property of antimicrobial agents acting on the cell wall. *Antimicrob Agents Chemother*. 1980;17:965–968.
104. Murray BE. Vancomycin-resistant enterococcal infections. *N Engl J Med*. 2000;342:710–721.
105. Galloway-Pena JR, Rice LB, Murray BE. Analysis of PBP5 of early U.S. isolates of *Enterococcus faecium*: sequence variation alone does not explain increasing ampicillin resistance over time. *Antimicrob Agents Chemother*. 2011;55:3272–3277.
106. al-Obeid S, Gutmann L, Williamson R. Modification of penicillin-binding proteins of penicillin-resistant mutants of different species of enterococci. *J Antimicrob Chemother*. 1990;26:613–618.
107. Montealegre MC, Roh JH, Rae M, et al. Differential penicillin-binding protein 5 (PBP5) levels in the Enterococcus faecium clades with different levels of ampicillin resistance. *Antimicrob Agents Chemother*. 2016;61:e02034–16.
108. Mainardi JL, Legrand R, Arthur M, et al. Novel mechanism of beta-lactam resistance due to bypass of DD-transpeptidation in *Enterococcus faecium*. *J Biol Chem*. 2000;275:16490–16496.
109. Murray BE, Mederski-Samoraj B, Foster SK, et al. In vitro studies of plasmid-mediated penicillinase from *Streptococcus faecalis* suggest a staphylococcal origin. *J Clin Invest*. 1986;77:289–293.
110. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing, 18th Informational Supplement. M100-S18*. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
111. Metzidie E, Manolis EN, Pournaras S, et al. Spread of an unusual penicillin- and imipenem-resistant but ampicillin-susceptible phenotype among *Enterococcus faecalis* clinical isolates. *J Antimicrob Chemother*. 2006;57:158–160.
112. Mederski-Samoraj BD, Murray BE. High-level resistance to gentamicin in clinical isolates of enterococci. *J Infect Dis*. 1983;147:751–757.
113. Zimmermann RA, Moellering RC Jr, Weinberg AN. Mechanism of resistance to antibiotic synergism in enterococci. *J Bacteriol*. 1971;105:873–879.
114. Kak V, Donabedian SM, Zervos MJ, et al. Efficacy of ampicillin plus arbekacin in experimental rabbit endocarditis caused by an *Enterococcus faecalis* strain with high-level gentamicin resistance. *Antimicrob Agents Chemother*. 2000;44:2545–2546.
115. Gavalda J, Len O, Miro JM, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. *Ann Intern Med*. 2007;146:574–579.
116. Fernandez-Hidalgo N, Almirante B, Gavalda J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *Enterococcus faecalis* infective endocarditis. *Clin Infect Dis*. 2013;56:1261–1268.
117. Mainardi JL, Gutmann L, Acar JF, et al. Synergistic effect of amoxicillin and cefotaxime against *Enterococcus faecalis*. *Antimicrob Agents Chemother*. 1995;39:1984–1987.
118. Arias CA, Singh KV, Panesso D, et al. Evaluation of ceftobiprole medocaril against *Enterococcus faecalis* in a mouse peritonitis model. *J Antimicrob Chemother*. 2007;60:594–598.
119. Nicas TI, Mullen DL, Flokowitsch JE, et al. Semisynthetic glycopeptide antibiotics derived from LY264826 active against vancomycin-resistant enterococci. *Antimicrob Agents Chemother*. 1996;40:2194–2199.
120. Baltch AL, Smith RP, Ritz WJ, et al. Comparison of inhibitory and bactericidal activities and postantibiotic effects of LY333328 and ampicillin used singly and in combination against vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 1998;42:2564–2568.
121. Allen NE, Nicas TI. Mechanism of action of oritavancin and related glycopeptide antibiotics. *FEMS Microbiol Rev*. 2003;26:511–532.
122. Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. *N Engl J Med*. 2014;370:2180–2190.
123. Dandekar PK, Tessier PR, Williams P, et al. Pharmacodynamic profile of daptomycin against *Enterococcus* species and methicillin-resistant *Staphylococcus aureus* in a murine thigh infection model. *J Antimicrob Chemother*. 2003;52:405–411.
124. Werth BJ, Steed ME, Ireland CE, et al. Defining daptomycin resistance prevention exposures in vancomycin-resistant *Enterococcus faecium* and *E. faecalis*. *Antimicrob Agents Chemother*. 2014;58:5253–5261.
125. Britt NS, Potter EM, Patel N, et al. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of vancomycin-resistant enterococcal bacteremia among Veterans Affairs patients. *Clin Infect Dis*. 2017;64:605–613.
126. Chuang YC, Lin HY, Chen PY, et al. Effect of daptomycin dose on the outcome of vancomycin-resistant, daptomycin-susceptible *Enterococcus faecium* bacteremia. *Clin Infect Dis*. 2017;64:1026–1034.
127. Sakoulas G, Bayer AS, Pogliano J, et al. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2012;56:838–844.
128. Sakoulas G, Rose W, Nonejuie P, et al. Ceftaroline restores daptomycin activity against daptomycin-nonsusceptible vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2014;58:1494–1500.
129. Arias CA, Torres HA, Singh KV, et al. Failure of daptomycin monotherapy for endocarditis caused by an *Enterococcus faecium* strain with vancomycin-resistant and vancomycin-susceptible subpopulations and evidence of in vivo loss of the *vanA* gene cluster. *Clin Infect Dis*. 2007;45:1343–1346.
130. Stevens MP, Edmond MB. Endocarditis due to vancomycin-resistant enterococci: case report and review of the literature. *Clin Infect Dis*. 2005;41:1134–1142.
131. Jenkins I. Linezolid- and vancomycin-resistant *Enterococcus faecium* endocarditis: successful treatment with tigecycline and daptomycin. *J Hosp Med*. 2007;2:343–344.
132. DiPippo AJ, Tverdek FP, Tarrand JJ, et al. Daptomycin non-susceptible *Enterococcus faecium* in leukemia patients: role of prior daptomycin exposure. *J Infect*. 2017;74:243–247.
133. Lesho EP, Wortmann GW, Craft D, et al. De novo daptomycin nonsusceptibility in a clinical isolate. *J Clin Microbiol*. 2006;44:673.
134. Arias CA, Panesso D, McGrath DM, et al. Genetic basis for in vivo daptomycin resistance in enterococci. *N Engl J Med*. 2011;365:892–900.
135. Munita JM, Tran TT, Diaz L, et al. A *liaF* codon deletion abolishes daptomycin bactericidal activity against vancomycin-resistant *Enterococcus faecalis*. *Antimicrob Agents Chemother*. 2013;57:2831–2833.
136. Munita JM, Panesso D, Diaz L, et al. Correlation between mutations in liaFSR of *Enterococcus faecium* and MIC of daptomycin: revisiting daptomycin breakpoints. *Antimicrob Agents Chemother*. 2012;56:4354–4359.
137. Shukla BS, Shelburne S, Reyes K, et al. Influence of minimum inhibitory concentration in clinical outcomes of *Enterococcus faecium* bacteremia treated with daptomycin: is it time to change the breakpoint? *Clin Infect Dis*. 2016;62:1514–1520.
138. Chong PP, van Duin D, Bangdiwala A, et al. Vancomycin-resistant enterococcal bloodstream infections in hematopoietic stem cell transplant recipients and patients with hematologic malignancies: impact of daptomycin MICs of 3 to 4 mg/L. *Clin Ther*. 2016;38:2468–2476.
139. Falagas ME, Siempos II, Vardakas KZ. Linezolid versus glycopeptide or beta-lactam for treatment of gram-positive bacterial infections: meta-analysis of randomised controlled trials. *Lancet Infect Dis*. 2008;8:53–66.
140. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy,

and management of complications: a scientific statement for healthcare professionals from the American heart Association. *Circulation*. 2015;132:1435–1486.

141. Whang DW, Miller LG, Partain NM, et al. Systematic review and meta-analysis of linezolid and daptomycin for treatment of vancomycin-resistant enterococcal bloodstream infections. *Antimicrob Agents Chemother*. 2013;57:5013–5018.
142. Chuang YC, Wang JT, Lin HY, et al. Daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bacteremia: systematic review and meta-analysis. *BMC Infect Dis*. 2014;14:687.
143. Balli EP, Venetis CA, Miyakis S. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. *Antimicrob Agents Chemother*. 2014;58:734–739.
144. Britt NS, Potter EM, Patel N, et al. Comparison of the effectiveness and safety of linezolid and daptomycin in vancomycin-resistant enterococcal bloodstream infection: a national cohort study of Veterans Affairs patients. *Clin Infect Dis*. 2015;61:871–878.
145. Britt NS, Potter EM, Patel N, et al. Effect of continuous and sequential therapy among veterans receiving daptomycin or linezolid for vancomycin-resistant *Enterococcus faecium* bacteremia. *Antimicrob Agents Chemother*. 2017;61:e02216–16.
146. Herrero IA, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant *Enterococcus faecium*. *N Engl J Med*. 2002;346:867–869.
147. Marshall SH, Donskey CJ, Hutton-Thomas R, et al. Gene dosage and linezolid resistance in *Enterococcus faecium* and *Enterococcus faecalis*. *Antimicrob Agents Chemother*. 2002;46:3334–3336.
148. Diaz L, Kiratisin P, Mendes RE, et al. Transferable plasmid-mediated resistance to linezolid due to *cfr* in a human clinical isolate of *Enterococcus faecalis*. *Antimicrob Agents Chemother*. 2012;56:3917–3922.
149. Sharkey LK, Edwards TA, O'Neill AJ. ABC-F proteins mediate antibiotic resistance through ribosomal protection. *MBio*. 2016;7:e01975.
150. Wang Y, Lv Y, Cai J, et al. A novel gene, *optrA*, that confers transferable resistance to oxazolidinones and phenicols and its presence in *Enterococcus faecalis* and *Enterococcus faecium* of human and animal origin. *J Antimicrob Chemother*. 2015;70:2182–2190.
151. Stein GE, Craig WA. Tigecycline: a critical analysis. *Clin Infect Dis*. 2006;43:518–524.
152. Namdari H, Tan TY, Dowzicky MJ. Activity of tigecycline and comparators against skin and skin structure pathogens: global results of the tigecycline evaluation and surveillance trial, 2004-2009. *Int J Infect Dis*. 2012;16:e60–e66.
153. Werner G, Gfrörer S, Fleige C, et al. Tigecycline-resistant *Enterococcus faecalis* strain isolated from a German intensive care unit patient. *J Antimicrob Chemother*. 2008;61:1182–1183.
154. Cattoir V, Isnard C, Cosquer T, et al. Genomic analysis of reduced susceptibility to tigecycline in *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2015;59:239–244.
155. Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis*. 2005;41(suppl 5):S341–S353.
156. Singh KV, Weinstock GM, Murray BE. An *Enterococcus faecalis* ABC homologue (Lsa) is required for the resistance of this species to clindamycin and quinupristin-dalfopristin. *Antimicrob Agents Chemother*. 2002;46:1845–1850.
157. Moellering RC, Linden PK, Reinhardt J, et al. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. Synercid Emergency-Use Study Group. *J Antimicrob Chemother*. 1999;44:251–261.
158. Matsumura S, Simor AE. Treatment of endocarditis due to vancomycin-resistant *Enterococcus faecium* with quinupristin/dalfopristin, doxycycline, and rifampin: a synergistic drug combination. *Clin Infect Dis*. 1998;27:1554–1556.
159. Lautenbach E, Schuster MG, Bilker WB, et al. The role of chloramphenicol in the treatment of bloodstream infection due to vancomycin-resistant *Enterococcus*. *Clin Infect Dis*. 1998;27:1259–1265.
160. Safdar A, Bryan CS, Stinson S, et al. Prosthetic valve endocarditis due to vancomycin-resistant *Enterococcus faecium*: treatment with chloramphenicol plus minocycline. *Clin Infect Dis*. 2002;34:E61–E63.
161. Perez Mato S, Robinson S, Begue RE. Vancomycin-resistant *Enterococcus faecium* meningitis successfully treated with chloramphenicol. *Pediatr Infect Dis J*. 1999;18:483–484.
162. Gupta K, Hooton TM, Roberts PL, et al. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med*. 2007;167:2207–2212.
163. Panesso D, Ospina S, Robledo J, et al. First characterization of a cluster of VanA-type glycopeptide-resistant *Enterococcus faecium*, Colombia. *Emerg Infect Dis*. 2002;8:961–965.
164. Schlegel L, Grimont F, Ageron E, et al. Reappraisal of the taxonomy of the *Streptococcus bovis/Streptococcus equinus* complex and related species: description of *Streptococcus gallolyticus* subsp. *gallolyticus* subsp. nov., *S. gallolyticus* subsp. *macedonicus* subsp. nov. and *S. gallolyticus* subsp. *pasteurianus* subsp. nov. *Int J Syst Evol Microbiol*. 2003;53:631–645.
165. Boleij A, van Gelder MM, Swinkels DW, et al. Clinical importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: systematic review and meta-analysis. *Clin Infect Dis*. 2011;53:870–878.
166. Ben-Chetrit E, Wiener-Well Y, Kashat L, et al. *Streptococcus bovis* new taxonomy: does subspecies distinction matter? *Eur J Clin Microbiol Infect Dis*. 2017;36:387–393.
167. Sillanpaa J, Nallapareddy SR, Singh KV, et al. Adherence characteristics of endocarditis-derived *Streptococcus gallolyticus* subs. *gallolyticus* (*S. bovis* biotype I) isolates to host extracellular matrix proteins. *FEMS Microbiol Lett*. 2008;289:104–109.
168. Corredoira-Sanchez J, Garcia-Garrote F, Rabunal R, et al. Association between bacteremia due to *Streptococcus gallolyticus* subsp. *gallolyticus* (*Streptococcus bovis* I) and colorectal neoplasia: a case-control study. *Clin Infect Dis*. 2012;55:491–496.
169. Sheng WH, Chuang YC, Teng LJ, et al. Bacteraemia due to *Streptococcus gallolyticus* subspecies *pasteurianus* is associated with digestive tract malignancies and resistance to macrolides and clindamycin. *J Infect*. 2014;69:145–153.
170. Boleij A, Muytjens CM, Bukhari SI, et al. Novel clues on the specific association of *Streptococcus gallolyticus* subsp *gallolyticus* with colorectal cancer. *J Infect Dis*. 2011;203:1101–1109.
171. Kumar R, Herold JL, Schady D, et al. *Streptococcus gallolyticus* subsp. *gallolyticus* promotes colorectal tumor development. *PLoS Pathog*. 2017;13:e1006440.
172. Gonzalez-Juanatey C, Gonzalez-Gay MA, Llorca J, et al. Infective endocarditis due to *Streptococcus bovis* in a series of nonaddict patients: clinical and morphological characteristics of 20 cases and review of the literature. *Can J Cardiol*. 2003;19:1139–1145.
173. Facklam R, Elliott JA. Identification, classification, and clinical relevance of catalase-negative, gram-positive cocci, excluding the streptococci and enterococci. *Clin Microbiol Rev*. 1995;8:479–495.
174. Endo A, Okada S. Reclassification of the genus *Leuconostoc* and proposals of *Fructobacillus fructosus* gen. nov., comb. nov., *Fructobacillus durionis* comb. nov., *Fructobacillus ficulneus* comb. nov. and *Fructobacillus pseudoficulneus* comb. nov. *Int J Syst Evol Microbiol*. 2008;58:2195–2205.
175. Buu-Hoi A, Branger C, Acar JF. Vancomycin-resistant streptococci or *Leuconostoc* sp. *Antimicrob Agents Chemother*. 1985;28:458–460.
176. Huang YT, Liao CH, Teng LJ, et al. Daptomycin susceptibility of unusual gram-positive bacteria: comparison of results obtained by the Etest and the broth microdilution method. *Antimicrob Agents Chemother*. 2007;51:1570–1572.

201 *Streptococcus agalactiae* (Group B Streptococci)

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SHORT VIEW SUMMARY

Definition
- Group B streptococci (GBS) are gram-positive bacteria that cause invasive hematogenous infection in at-risk individuals.

Epidemiology
- GBS asymptomatically colonize the lower gastrointestinal or genital tract in approximately one-fourth to one-third of men and women.
- Distribution is worldwide, but rates vary geographically.
- Disease burden from GBS disease is increasing, especially in adults with underlying conditions including diabetes mellitus and persons with chronic liver or kidney disease; cancer, heart, or cardiovascular conditions; or neurologic impairment.
- Nursing home residents have a markedly higher incidence of invasive GBS disease than do community-dwelling adults.

Microbiology
- β-Hemolytic streptococci exhibit a narrow zone of hemolysis on blood agar.
- GBS have a polysaccharide capsule with pilus-like structures that enhance adherence and invasion.
- GBS grow readily in blood culture media and specimens from cerebrospinal fluid and other sites of infection.

Diagnosis
- In adults, onset is acute, with chills and fever, or acute-on-chronic, with indolent symptoms, especially in association with skin and soft tissue manifestations.
- In infants younger than 3 months, bacteremia without a focus; meningitis; or, less often, other focal infections, such as pneumonia or soft tissue infection, occur.
- Growth of GBS from blood or another normally sterile site is diagnostic.

Treatment
- Penicillin is the drug of choice; isolates are uniformly susceptible to β-lactams and meropenem. Isolates are generally susceptible to vancomycin; there have been only a few case reports of resistance.
- The duration of treatment ranges from 10 days for uncomplicated bacteremia to a 4-week minimum treatment course for endocarditis.

Prevention
- Intrapartum antibiotic prophylaxis given to colonized parturients during labor prevents early-onset infections in neonates, thus reducing the overall rate of neonatal sepsis (see Table 201.3).
- Both glycoconjugate and protein-based vaccines are in clinical trials and offer the potential for prevention of infections in pregnant women, neonates, and young infants, and invasive infections in nonpregnant adults.

HISTORICAL PERSPECTIVE

Group B streptococci (GBS; *Streptococcus agalactiae*) were reported as human pathogens in 1938 by Fry, who described three cases of fatal puerperal sepsis.[1] Infections in humans were reported infrequently until the 1960s, when it became evident that disease was occurring more commonly.[2] By the 1970s, GBS emerged as the predominant pathogens causing septicemia and meningitis in neonates and young infants and as a cause of substantial pregnancy-related morbidity. Implementation of maternal intrapartum chemoprophylaxis in the mid-1990s resulted in a dramatic decrease in early-onset neonatal disease incidence and in a decline in invasive disease during pregnancy.[3]

In the past nearly 3 decades, twofold to fourfold increases in the incidence of group B streptococcal disease have occurred in nonpregnant adults; most of these patients have had underlying medical conditions or are 65 years of age or older.[4,5] Active, population-based surveillance indicates that more than 90% of invasive group B streptococcal disease cases now occur in nonpregnant adults.[3,6] The highest case-fatality rate as a consequence of group B streptococcal infection is among nonpregnant adults older than 65 years.[7] These shifts in incidence and outcome suggest that at-risk adults might benefit from immunization with a group B streptococcal glycoconjugate vaccine, should this vaccine become available commercially. Publication of the complete genome sequences of major GBS capsular types opened new avenues for the identification of novel vaccine targets and for further elucidating the molecular basis for virulence of the organism.[8,9]

DESCRIPTION

Classification and Morphologic Characteristics

S. agalactiae is the species designation for streptococci belonging to Lancefield group B. The serologic differentiation of β-hemolytic streptococci by groups is based on capillary precipitin reactions between the group-specific carbohydrate cell wall antigen and hyperimmune rabbit antisera. GBS are facultative, gram-positive diplococci that grow on a variety of culture media. Isolated colonies on sheep blood agar are 3 to 4 mm in diameter and grayish white. The flat, somewhat mucoid colonies are surrounded by a narrow zone of β-hemolysis. One percent to 2% of strains are nonhemolytic. Selective media have been used to enhance the accurate detection of low numbers of GBS from sites such as the genital or gastrointestinal (GI) tract. These usually contain Todd-Hewitt broth with or without sheep red blood cells and antimicrobial agents, such as nalidixic acid and gentamicin or colistin, or chromogenic agar.

Identification

Definitive identification of GBS is based on detection of the group B–specific cell wall antigen common to all strains. A number of serologic methods using hyperimmune group B–specific antisera are used for detection of the group B antigen. Latex agglutination is the most widely used. When the manufacturer's instructions are followed, these products are comparable to the Lancefield capillary precipitin method.

Biochemical methods that permit the presumptive identification of GBS include resistance to bacitracin or trimethoprim-sulfamethoxazole, positive sodium hippurate hydrolysis, and the production of an orange pigment during anaerobic growth on certain media. Production of CAMP (Christie, Atkinson, Munch, Peterson) factor, a thermostable extracellular protein that results in synergistic hemolysis on sheep blood agar with the β-lysin of *Staphylococcus aureus,* is observed in 98% to 100% of GBS. The combination of the CAMP test with bacitracin susceptibility testing and the bile esculin reaction is adequate for presumptive differentiation of GBS from other serogroups of β-hemolytic streptococci.

Serologic Typing

GBS are differentiated serologically by capsular polysaccharide type and by cell surface–expressed proteins. Lancefield defined two cell wall carbohydrate antigens, the group B–specific or C substance, common to all strains, and the S substance, which allowed classification into types I, II, and III.[10] Later, she reported differences in type I strains and designated these Ia and Ib.[11] These strains possessed capsular polysaccharide Ia or Ib, and some strains also had a surface protein designated C protein, subsequently found to have α and β components. The nomenclature was revised in 1984 to designate the capsular polysaccharides as type antigens, with surface proteins as additional markers.[12] Additional capsular types, IV through IX, have been defined, and additional candidates are being evaluated.

The α C protein is the prototype for a family of proteins (α-like proteins) that includes Rib and Alp1 to Alp4 and is found in most GBS. R proteins (R1 to R4) are found on some strains. Each of the common polysaccharides has a characteristic protein expression pattern, but exceptions occur. For example, Alp1 is found frequently in type Ia strains, Rib is most often associated with type II and III strains, and Alp3 is associated with type V strains.[13] The β C protein binds to human immunoglobulin A (IgA) and is found mainly in type Ib strains.

Antibodies directed against polysaccharide antigens were shown by Lancefield to provide passive protection in mice challenged with homologous, but not heterologous, antigen-containing strains.[14] The α and β C proteins and Rib also elicit protective antibodies in animals,[15,16] but their role in human infections is not known. Antibodies directed at the group B antigen are not protective.

GBS consist of a large and diverse core population from which recombinant clones with limited diversity have emerged with properties that have allowed them to successfully disseminate and adapt to a special habitat, such as that of the human neonate.[17] The classic method for capsular typing of GBS is by capillary precipitins or immunodiffusion in agarose between acid extracts of the organism and hyperimmune rabbit antisera. Molecular assays for capsule type identification include multilocus sequencing typing, pulsed gel electrophoresis, and polymerase chain reaction (PCR). PCR-based and whole-genome sequencing methods offer powerful tools to document the epidemiologic relatedness of strains and to distinguish among the known types.[18–20] Such methods can determine whether recurrent infections are caused by separate or identical strains and can identify virulent clone families that may be disproportionate causes of invasive disease.[20] Molecular methods do not permit an assessment of polysaccharide or protein expression. However, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has allowed rapid detection of proteins specific for highly virulent strains.[21]

EPIDEMIOLOGY AND TRANSMISSION

Asymptomatic Colonization

GBS colonize the genital area or lower GI tract of women at rates ranging from 10% to 40%; in men, GI tract carriage is estimated to be 10% to 25%. Variations in prevalence of asymptomatic colonization relate to sites sampled, methods of detection, and demographic differences in populations (Table 201.1). When multiple appropriate sites, such as the lower vagina or the periurethral area *and* the rectum, are sampled and when the selective broth media are used, colonization rates typically exceed 20%. The association of GBS with asymptomatic bacteriuria during pregnancy is a marker for a high density of organisms or heavy genital colonization.

Colonization with GBS occurs more frequently among black women than in other racial or ethnic groups. Diabetes mellitus also is independently associated with higher rates of group B streptococcal colonization during pregnancy. Multiple partners and frequent or recent sexual intercourse are associated with increased risk for vaginal acquisition over time, possibly because sexual activity alters the vaginal microenvironment to make it more permissive for colonization. Sexual activity and particularly male-to-female oral sex increase the risk for cocolonization with identical group B streptococcal strains in heterosexual college couples.[22] Sexually inexperienced persons have low genital colonization rates. Pregnancy does not influence colonization prevalence.

TABLE 201.1 Factors Influencing Detection of Group B Streptococcal Colonization

	EFFECT ON ISOLATION RATE		
	INCREASED	**DECREASED**	**NONE**
Method Used			
Culture medium	Broth media Antibiotic-containing media	Agar media Nonselective broth media	— —
Sites in women	Lower vagina and rectum	Cervical os	—
Sites in infants and adults	Multiple sites	Single site	—
Interval	Two or more cultures in interval of 6–8 wk	Single sampling time	—
Genital Carriage in Women			
Pregnancy	—	—	+
Time during pregnancy	—	—	+
Day of menstrual cycle	First half	—	—
Age	≤20 yr	—	—
Sexual activity	Active	No sexual debut	—
Frequency of sexual intercourse or total number of partners	+	—	—
Vaginal discharge	—	—	+
Birth control method	Intrauterine device	—	Oral contraceptives
Parity	Primigravida	More than three pregnancies	—
Ethnic origin	Black	Asian	—
Marital status	—	—	+
Socioeconomic group	Lower income	—	—

+, Documented to have effect indicated on isolation rate.

The principal reservoir for GBS is the lower GI tract. The presence of GBS in the GI tract is a risk factor for vaginal colonization.[23] Changes in capsule expression and recolonization with antigenically distinct group B streptococcal clones can occur over time, and specific sequence types associated with loss or persistence of colonization have been defined.[24] The prevalence of oropharyngeal colonization in adults is about 5% but can approach 20% in men who have sex with men. The colonization rate in healthy older adults is about 20%.[25]

Transmission

Maternal-to-infant transmission occurs in utero by the ascending route or at the time of delivery. Vaginally colonized pregnant women are at an increased risk for premature labor. The rate of vertical transmission among neonates born to women colonized with GBS who do not receive intrapartum antibiotic prophylaxis before delivery is about 50%. A high maternal genital inoculum at delivery significantly increases the likelihood of vertical transmission. Transmission also can occur within the hospital setting, albeit uncommonly, likely through hand-to-hand contact, and in closed populations such as nursing homes.

Incidence and Serotype Distribution of Isolates

The mean incidence of invasive group B streptococcal disease globally in infants younger than 3 months is estimated to be approximately 0.5 cases per 1000 live births.[26] There is marked variation by geographic

region, with higher rates in Africa, followed by the Americas and Europe, and the lowest rates in Southeast Asia.[27,28,29] The incidence of early-onset (0 through age 6 days) neonatal group B streptococcal infection in the United States, formerly 1 to 3 per 1000 live births, declined by 2016 to 0.21 per 1000 live births in association with widespread use of antenatal culture screening and intrapartum antibiotic prophylaxis for colonized women.[30,31] Use of this prevention strategy has had no impact on late-onset (age 7 through 89 days) disease incidence, which still occurs at a rate of approximately 0.3 per 1000 live births.

The incidence of invasive disease in pregnancy declined significantly in association with the use of intrapartum antibiotic prophylaxis, but pregnancy-associated group B streptococcal disease is responsible for peripartum febrile morbidity. Intrapartum vaginal colonization with GBS also is an independent risk factor for intraamniotic infection. Women with "heavy" (≥50 colonies on the primary blood agar plate) or high-inoculum GBS colonization are at significantly greater risk for intraamniotic fluid infection than those with "light" (1–10 colonies) vaginal colonization. Among women with invasive group B streptococcal disease for whom pregnancy outcome was known, 61% had a spontaneous abortion or a stillborn infant, 30% had infants without apparent illness, 5% had live-born infants who developed clinical infections, and 4% had induced abortions.[30]

Invasive group B streptococcal disease among nonpregnant adults has been increasing for decades.[6] Adults now account for in excess of 90% of all invasive group B streptococcal disease cases in the United States.[31] Most adults have at least one predisposing medical condition, such as diabetes mellitus, chronic liver or renal disease, human immunodeficiency virus infection, malignancy, or stroke. The incidence of adult disease increased from 3.6 cases per 100,000 population in 1990 to 10.9 cases per 100,000 population in 2016.[32,32a] An estimated 27,700 cases of invasive disease and 1500 deaths occurred in the US population in 2016. A multinational population-based assessment found that bloodstream infection rates increased among older adults across all study regions, especially in association with diabetes.[33] In one population-based surveillance report, adults 65 years of age and older represented one-third of cases of invasive group B streptococcal disease. Nursing home residents have a markedly higher incidence (72 per 100,000 population) than community residents 65 years of age and older.[7]

Group B streptococcal types Ia, III, and V represent more than two-thirds of colonizing isolates in pregnancy and the same proportion of isolates in early-onset neonatal disease. Late-onset infant disease is caused predominantly by type III strains.[30] Among nonpregnant adults, type Ia strains account for 23% of almost 2000 cases of invasive disease in 2016, followed by types II and V (18% each), Ib (15%), III (12%) and IV (11%).[32a] Serotypes Ia, Ib, II, III, and V accounted for 86% and 94%, respectively, of invasive strains in nonpregnant adults in contemporary surveillance studies in the United States and France.[33,34] In Brazil, a surveillance study confirmed the high prevalence of the same serotypes but showed regional variability in the distribution of serotypes.[35] Types IV, VI through VIII, and nontypable isolates are uncommonly associated with invasive infection, but in Japan serotypes VI and VIII are frequently isolated from pregnant women.[36] Type IV strains are increasing as a cause of invasive disease in adults globally[37,38]

PATHOGENETIC MECHANISMS

Adherence

To cause disease, GBS must colonize mucosal surfaces and then breach these surfaces to enter normally sterile sites such as the bloodstream. GBS have surface-exposed protective antigens that are components of high-molecular-weight, covalently linked, pilus-like structures, and these structures contribute both to adherence and to invasion of host cells.[39]

GBS adhere to several human cells, including vaginal and intestinal epithelium, placental membranes, respiratory tract epithelium, and the blood-brain barrier endothelium. A role for the α protein is proposed in the interaction between the bacterium and the host cell.[40] The α protein is a prototype for a family of long, tandem repeat–containing surface proteins that are common to GBS types causing most invasive disease. The pilus operon codes for three proteins that contain the conserved amino-acid motif LPXTG (leucine, proline, any amino acid, threonine, glycine), associated with cell wall–anchored proteins, together with two genes coding for sortase enzymes.[39] Genes encoding the surface-associated pili have a role in adhering to cell surfaces such as brain endothelium.[41] The widely conserved, surface-exposed fibrinogen receptor FbsA also promotes adherence of GBS to human epithelial cells.[42]

Invasion

GBS can cross the epithelial barrier by a paracellular route, and translocation of epithelial barriers is proposed as the predominant route for dissemination of the organism in the human host.[43,44] In support of this mechanism, pili can locate in the intercellular space ahead of translocating bacteria. That pilus backbone also contributes to paracellular translocation of GBS is supported by experiments in which deletion of the pilus backbone protein reduces the capacity of the organism to transcytose through differentiated human epithelial cells.[45]

GBS can invade respiratory epithelial and endothelial cells and brain microvascular endothelial cells in vitro.[46] It is proposed that α C protein mediates translocation across epithelial barriers by facilitating intracellular invasiveness through binding to glycosaminoglycan on the surface of the host cell.[47] Proper anchoring of lipoteichoic acid on the group B streptococcal surface facilitates invasion,[48] and the group B streptococcal pore-forming β-hemolysin/cytolysin also promotes invasion of lung epithelial cells.[49] β-Hemolysin/cytolysin expression also correlates with lung epithelial cell injury and promotes injury of lung microvascular endothelial cells, increasing cell permeability in vitro. This increased permeability contributes to alveolar edema and hemorrhage that could be a feature of group B streptococcal pneumonia.[50]

Bacterial Virulence Factors

GBS produce a capsule that inhibits complement deposition and phagocytosis. Strains that effectively evade host phagocytes can damage tissues by inducing the release of inflammatory modulators or by production of substances that directly damage cells. A high quantity of cell-associated sialic acid and its elaboration in supernatant fluid are associated with virulence of type III strains.[51] Population studies reveal a strong correlation of capsular polysaccharide type III with CC17 hypervirulent strains that are documented to cause invasive neonatal disease worldwide.[52] Changes in capsular expression are associated with a loss of virulence in experimental models of lethal infection. The unique structures of GBS capsules also may enhance the invasiveness of one capsular type over another. A novel insertion sequence in the hyaluronidase gene has been identified predominantly in group B streptococcal strains causing endocarditis.[53] The mechanism by which this genetic alteration and the lack of hyaluronidase increase disease potential is speculative.

The pore-forming β-hemolysin/cytolysin enhances virulence by promoting invasion and cell injury and by inducing cytolysis and apoptosis of phagocytes in concert with shielding by carotenoid of GBS from oxidative damage.[54] Hyperhemolytic variants promoted joint injury compared with a nonhemolytic group B streptococcal variant in a murine model of infection. Group B streptococcal β-hemolysin/cytolysin also directly impairs cardiomyocyte viability and function,[55] and hyperhemolytic strains can disrupt the amniotic barrier and penetrate placental membranes.[56] The surface-localized β protein binds human complement factor H, and the complexed factor H retains its ability to downregulate complement activation.[57] In addition, *cspA,* a novel gene that encodes a surface-localized, serine protease–like protein, has been identified. It promotes group B streptococcal survival by evasion of opsonophagocytosis and is required for group B streptococcal cleavage of fibrinogen.[58]

Host Factors

Baker and Kasper[59] reported in 1976 that neonates and young infants at risk for invasive type III group B streptococcal infection were those with low concentrations of passively acquired maternal antibodies to the type III capsular polysaccharide. Women colonized with type III GBS who delivered healthy neonates had higher concentrations of type III–specific IgG than women whose infants developed early-onset type III disease. A low concentration of maternal antibodies to other capsular polysaccharides also is a determinant of neonatal susceptibility to infection. Colonization is a dynamic process, however. In longitudinal studies

during pregnancy, the average duration of colonization is about 6 weeks, so duration of colonization per se does not predict maternal immunity.

Little is known regarding host factors that predispose adults to develop group B streptococcal infection. A broad range in concentration of antibodies to the capsular polysaccharide of the infecting strain is found in acute-phase sera from adults with invasive infection. Some adults already have relatively high concentrations of antibodies to the infecting capsular polysaccharide when illness occurs. As a group, nonpregnant adults demonstrate an immune response to capsular polysaccharides and to pilus proteins during recovery from invasive infection, but whether these function to protect against infection is unknown.[60] Although anticapsular antibody may be protective in many cases, the susceptibility of some adult patients to group B streptococcal infection may be the result of defects in other aspects of the host defense, such as phagocytosis.

CLINICAL MANIFESTATIONS

Invasive group B streptococcal infection causes substantial morbidity and mortality, and the disease burden is increasing, especially among older persons, blacks, and adults with diabetes.[30] In a prospective, population-based assessment of invasive group B streptococcal disease, adults accounted for 92% of cases.[30] Adults with bacteremia unrelated to pregnancy are often elderly, but ages range from 18 to 103 years.[61–67,32a] The mean age in one report was 63 years, and 59% were men. The incidence increases with age, is higher in blacks than in other races or ethnicities, and is increased among elderly adults in long-term care facilities compared with community-dwelling older adults.[68]

One or more medical conditions predisposing to infection are present almost uniformly in adults with invasive disease (Table 201.2). In a multistate, population-based survey, 95% of cases occurred in persons with at least one underlying condition, most often obesity (54%), diabetes (53%), or neurologic disease (26%). Smoking, cardiovascular disease, renal disease, immunosuppressive conditions, liver disease, and lung disease also were underlying conditions.[32a] Among patients with soft tissue infections, ~40% report diabetes mellitus as a comorbid condition.[67] Neurologic illnesses associated with invasive infections include dementia, cerebrovascular disease causing altered mental status, and paraplegia or quadriplegia. Young adults (20–40 years of age) with diabetes, cancer, or human immunodeficiency virus (HIV) infection are at significantly increased risk (28- to 30-fold) for invasive disease.[6] Hospital-associated infection was independently associated with placement of a central venous line, diabetes, congestive heart failure, and seizure disorder.[68] Age 65 years or older is a risk factor for invasive group B streptococcal infection. The incidence doubles when 50- to 64-year-olds are compared with those 65 years of age and older.[67] Among a group of community-dwelling older adults, the age-specific incidence increased steadily and was about threefold higher in those older than 85 years than in a 65- to 74-year-old group.

Mortality is increased in older patients, in those with polymicrobial infection, and in patients with diabetes mellitus, liver disease, or malignancy. Contemporary case-fatality rates in nonpregnant adults range from 5% to 25%. Shock at diagnosis, alcoholism, and cancer are associated independently with an increased risk for death.[69] Nursing home residents are more likely to have a fatal outcome than are community-dwelling older adults. Health care–associated infection can occur, but case clustering has not been observed. The latter suggests that endogenous respiratory, genitourinary, or GI colonization, rather than the acquisition of GBS in the hospital, is the source of infection. About one-fourth of patients with GBS isolated from the bloodstream have polymicrobial bacteremia. *S. aureus* is a frequently observed second isolate. The age distribution, mortality rate, and proportion of health care–associated cases do not differ between patients with bacteremia caused only by GBS and those with polymicrobial bacteremia.[68]

Most group B streptococcal infections manifest with one of several clinical expressions of infection.

Primary Bacteremia

The most common presenting manifestations of nonfocal infections in adults are fever, chills, and change in mental status.[70] When no evident site of infection can be established, patients from whom GBS have been isolated from blood are considered to have primary bacteremia. Primary bacteremia can account for 20% to 50% of cases, and this manifestation carries a high fatality rate. Among survivors, recurrence of infection can occur in which a focus of infection is identified, such as endocarditis or osteomyelitis.[71]

Infections of the Female Genital Tract

In adults, a substantial number of infections caused by GBS are associated with pregnancy. The female genital tract is the source of these infections. GBS alone or as a component of a polymicrobial infection is among the most commonly isolated facultative aerobes from women with early postpartum endometritis. One-half of cases of pregnancy-associated bacteremia are associated with infection of the upper genital tract, placenta, or amniotic fluid, resulting in fetal death. Other manifestations include bacteremia without a focus in one-third of women, endometritis without fetal death, chorioamnionitis without fetal death, pneumonia, and puerperal sepsis.[30] Overall, GBS account for an estimated 15% of cases of peripartum endometritis, 15% of pregnancy-associated bacteremias, and up to 15% of wound infections after cesarean section.[72]

Focal signs and symptoms of infection usually develop within 48 hours after delivery. Among patients who deliver abdominally, women colonized with GBS have a significantly increased frequency of premature rupture of membranes, postpartum fever, and endometritis when compared with noncolonized women. The clinical findings of endometritis are nonspecific and include fever greater than or equal to 100.4°F with or without chills, malaise, moderate uterine tenderness, and normal lochia. Life-threatening sequelae of endometritis, such as pelvic abscess, septic shock, or septic thrombophlebitis, can occur, albeit rarely. Another manifestation of morbidity from group B streptococcal infection in pregnant women is urinary tract infection. Bacteriuria typically is asymptomatic or, less often, can manifest as cystitis or, rarely, pyelonephritis.

The role of GBS as an etiologic agent causing vaginitis has not been established. It is regarded as a commensal organism in the vagina and does not elicit a vaginal inflammatory response. Anecdotal reports suggest the pathogenic potential of GBS in vaginitis and resolution of symptoms of vaginitis in association with a short course of antibiotic administration.[73]

There is growing evidence to suggest that preterm birth is associated with maternal group B streptococcal colonization, especially when there

TABLE 201.2 Underlying Conditions in Invasive Group B Streptococcal Infections

CONDITION	*n* (%)
Diabetes mellitus	82 (30)
Liver disease or history of alcohol abuse	66 (24)
Neurologic impairment	58 (21)
Malignancy	52 (19)
Renal insufficiency or failure	37 (14)
Cardiovascular disease or heart failure	37 (14)
Pulmonary disease	21 (8)
Urologic disease	11 (4)
Peripheral vascular disease	9 (3)
Human immunodeficiency virus infection	7 (3)
Intravenous catheter-related infection	5 (2)
Gastrointestinal disease	5 (2)
Steroid administration	5 (2)
Hypertension	4 (1)
Functional or surgical splenectomy	3 (1)
Other	7 (3)
None	5 (2)

[a]*N* = 271 adults. Streptococcal infections listed were not related to pregnancy. Some patients had more than one underlying condition.
From references 5 and 61–65.

is evidence of ascending infection. In cohort studies, preterm birth is associated with maternal bacteriuria.[74] Among the estimated 2.6 million stillbirths globally each year, GBS is associated with approximately 1% of all stillbirths in developed countries and 4% of those in South Africa.[75]

Infections in Infants

Early-onset infection, occurring in neonates younger than 7 days, has a mean onset at 12 hours of age. Maternal obstetric complications are common, and infants born at less than 37 weeks' gestation have significantly higher attack rates than those born at term. Bacteremia or septicemia, pneumonia, and meningitis are the common clinical expressions of infection, and they occur at frequencies of about 85%, 10%, and 5%, respectively.[30] The presenting signs are nonspecific and are indistinguishable from those in neonates with bacterial infections of other causes. Signs of respiratory distress are observed in most infants. In the era of maternal screening, virtually all cases of early-onset disease occur in infants whose mothers have silent or clinically overt intraamniotic infection and in those who either did not receive intrapartum antibiotic prophylaxis during preterm labor or were negative for group B streptococcal colonization at screening culture at 35 to 37 weeks of gestation.[76]

Late-onset infection has an onset between 7 and 89 days of age, with a median of 36 days.[77] Currently, about 30% of the infants with late-onset disease in the United States are born prematurely. Other maternal obstetric complications are uncommon, and the case-fatality ratio is 3% to 5%.[30] Bacteremia and meningitis are common manifestations of infection, but focal infections, including osteomyelitis, septic arthritis, or cellulitis, can occur. Infants can present with fulminant infection characterized by rapid progression to a moribund state with septic shock and seizures. Among survivors of group B streptococcal meningitis, whether onset is early or late, approximately 50% have permanent neurologic sequelae.[78]

Pneumonia

Patients with group B streptococcal pneumonia have in common the apparent inability to limit the spread of the organism from colonizing mucous membrane sites to the bloodstream. The most common underlying medical conditions among these adult patients are diabetes mellitus and neurologic disease. These patients are often debilitated and bedridden. Fever, leukocytosis, and hypoxia are common presenting features. Chest radiographs can show bilateral or lobar infiltrates. Pleural empyema can occur. Fatality rates in patients with pneumonia range from 30% to 85%.

Endocarditis

A shift in the clinical expression of group B streptococcal endocarditis was first documented by Lerner and colleagues.[64] In contrast to the predominance of acute endocarditis in pregnant women during the preantibiotic era, cases reported since 1945 have had no gender predilection, have been both acute and subacute in onset, and have occurred in older patients (mean age, about 50 years). The mitral valve most often is affected (48%); infections involving the aortic (29%), mitral and aortic (10%), and tricuspid valves (5%) also have been described. Tricuspid valve involvement typically occurs in injection drug users. Prosthetic valve endocarditis has been noted.[79] Underlying heart disease exists in most cases, and valvular disease, atherosclerotic or rheumatic heart disease, and mitral valve prolapse each can be predisposing conditions.[80] An aggressive course with large friable vegetations is a frequent feature of group B streptococcal endocarditis.[81] Vegetations can resemble atrial myxomas, and embolization can occur early in the clinical course. Rapid valve destruction can necessitate early valve replacement in some patients.[82] The mortality rate is about 35% to 50%.

Arthritis

Group B streptococcal arthritis is monoarticular in two-thirds of patients and involves more than one joint in the remainder. In a review of 75 adults with group B streptococcal arthritis in which patients with prosthetic joint infection were excluded, the mean age was 58 years, and 45% were men.[83] The most commonly affected joints, in descending order of frequency, were the knee, shoulder, hip, and sternoclavicular and sacroiliac joints. One or more underlying medical conditions were present in three-fourths of patients, most commonly diabetes mellitus, malignancy, or chronic liver disease. One-third had a nonjoint focus of group B streptococcal infection, such as vertebral osteomyelitis or urinary tract infection. The most common presenting features were fever and joint pain, but about 14% of patients were afebrile. The erythrocyte sedimentation rate, when performed, was more than 30 mm/h in 95% of patients, and GBS were isolated from blood cultures in two-thirds. Surgical drainage was performed in 36% of cases.

Group B streptococcal prosthetic joint infections (≈75% of cases) usually occur 3 or more months after implantation and are usually (>90%) associated with comorbidities. In one review of 34 patients with prosthetic hip or knee infections, all patients underwent surgery.[84] Fifteen patients were treated with débridement with retention of the implant (relapse occurred in 2), 3 with a one-stage exchange arthroplasty, and 12 with a two-stage exchange, and 4 required removal of the implant. With appropriate antimicrobial therapy, the infection was cured in most patients, and functional mobility was preserved in more than 80%.

Osteomyelitis

Osteomyelitis occurs as a consequence of adjacent arthritis, peripheral vascular disease, orthopedic surgery, or an adjacent focus of infection. In a review of 39 cases of group B streptococcal osteomyelitis, one-half of the episodes were diagnosed as acute and one-half as chronic.[85] The mean age was 56 years, one-third of patients were older than 65 years, and two-thirds were men. The most commonly affected bones were the vertebrae, followed in order of frequency by the foot, bones around the hip, tibia, and toes. Underlying medical conditions were almost invariably present, most commonly diabetes mellitus, previous bone surgery, prosthetic bone or joint, or peripheral vascular disease. Foot bone involvement occurred predominantly in diabetic patients. Bones around the hip were involved in association with prior surgical procedures or trauma to the hip joint.

No specific clinical signs were associated with group B streptococcal osteomyelitis. The majority of patients were afebrile and had a normal erythrocyte sedimentation rate at the time of presentation. Cultures of bone or blood yielded GBS in about 90% and 40% of patients, respectively. Approximately one-fourth of infections are polymicrobial, with *S. aureus* or Enterobacteriaceae the most commonly associated microorganisms.[86] Most patients require a combined medical and surgical approach. The mean duration of antibiotic therapy is 10 weeks. Fatal infections are uncommon, but amputation may be required for resolution of infection in some patients with vascular insufficiency.

Skin and Soft Tissue Infections

Skin and soft tissue are the most common focal group B streptococcal infections in adults, accounting for more than one-third of infections. In these patients the diagnosis is most often made through isolation of the organism from one or more blood cultures and/or a surgical site tissue specimen. Cellulitis, foot ulcers, abscess, and infection of decubitus ulcers are frequent manifestations (Fig. 201.1). Cellulitis has occurred in association with foreign bodies, such as breast or penile implants. Relapsing cellulitis occurs in individuals with skin affected by chronic lymphedema.[87] Less common manifestations of skin and soft tissue infections are pyomyositis, blistering dactylitis, and necrotizing fasciitis, on occasion associated with toxic shock–like syndrome.[88,89] There are no features of these infections unique to GBS except that underlying conditions, such as diabetes mellitus and obesity, generally exist.

Meningitis

Meningitis caused by GBS has been reported in adults, most of whom have predisposing comorbid conditions.[90,91] The mean age of nonpregnant adults is 52 years; almost one-half are men. Several have had proven or possible disruption of the anatomic barrier protecting the brain as a consequence of surgery for tumors or chronic sinusitis. The overall case-fatality rate is 34%. Advanced age and overwhelming illness with presenting features such as coma or septic shock are associated with a poor outcome. Deafness, reported in 7% of survivors, is the most common neurologic sequela.

FIG. 201.1 Recurrent lower extremity cellulitis in a 70-year-old man who had undergone a saphenous venectomy.

Urinary Tract Infections

The spectrum of group B streptococcal urinary tract infection includes asymptomatic bacteriuria, cystitis, urethritis, pyelonephritis, and urosepsis. Asymptomatic bacteriuria during pregnancy is a surrogate for heavy maternal vaginal colonization. Clinically, urinary tract infections caused by GBS are not distinctive. Symptoms are consistent cystitis in approximately 80% and pyelonephritis in approximately 20% of patients.[92] Most infections are community acquired, occurring in middle-aged women, most of whom have an underlying condition such as alteration of urinary flow or stones. Symptomatic infection is common among residents of long-term care facilities. Treatment failure or relapse can occur, most likely as a consequence of persistent vaginal or enteric colonization.

Uncommon Manifestations of Infection

GBS, alone or as a component of mixed infection, have been isolated from a number of patients with keratitis or endophthalmitis. These infections occurred in eyes with severely damaged surfaces; the outcome was poor, with light perception being lost in one-half of the affected eyes.[93] Other unusual infections caused by GBS include breast abscess in a nonlactating woman,[94] ventriculoperitoneal shunt infection,[95] spinal epidural abscess,[96] mycotic aneurysm,[97] liver abscess,[61] intraabdominal abscess,[98] peritonitis,[4,64] and infection of a pacemaker wire after sigmoidoscopy.[99] GBS also have been reported to cause a toxic shock–like syndrome.[100]

Recurrent Invasive Group B Streptococcal Infection

Four percent to 7% of nonpregnant adults who survived an episode of group B streptococcal bacteremia had a recurrence.[32a,71] The mean interval between episodes of bacteremia is 24 weeks, but the interval is shorter when the recurrent episode is caused by the same capsular type (mean, 14 weeks) than when it is caused by another serotype (mean, 43 weeks between episodes). Several patients in whom primary bacteremia was the diagnosis of the first episode presented with focal infection, such as endocarditis or osteomyelitis, during the second episode.

DIAGNOSIS

Isolation of GBS from blood, cerebrospinal fluid, another usually sterile site, or a site of focal suppuration is the only means by which the diagnosis of invasive infection can be documented. Recovery of the organism from mucous membrane sites is of no diagnostic significance.

Intrapartum detection of colonization with GBS in women presenting for delivery can assist in identifying at-risk patients who will benefit from intrapartum chemoprophylaxis or empirical treatment. One fluorogenic real-time PCR technique for rapid detection of GBS in pregnant women at delivery had a sensitivity of 97% and a specificity of 100% when compared with cultures of vaginal and rectal swabs inoculated into selective broth medium.[101] Results were available in 45 minutes, compared with 100 minutes for conventional PCR and 36 hours or longer for the conventional culture technique. Field testing of commercially manufactured assays such as the Xpert GBS Assay (Cepheid, Sunnyvale, CA), which uses automated real-time PCR technology, and IDI-Strep B (Infectio Diagnostic, Quebec, Canada), which uses a PCR assay to amplify GBS-specific DNA and a fluorogenic probe to detect the amplified group B streptococcal target, has been performed.[102,103] When compared with conventional culture methods, these assays are sufficiently robust to be performed for intrapartum patients in point-of-care settings but have not replaced the culture-based method used for antenatal identification of women who are colonized with GBS as candidates for intrapartum antibiotic prophylaxis to prevent early-onset neonatal infection.

TREATMENT

GBS remain susceptible to penicillins and cephalosporins in vitro, although several strains with somewhat reduced susceptibility to penicillin have been identified in Japan.[104] Penicillin G is the drug of choice. The organism also is susceptible to vancomycin, meropenem, and imipenem. There have been recent reports of vancomycin-resistant strains associated with invasive disease in the United States.[105] Rates of fluoroquinolone resistance are variable and are associated with mutations in the gyrase and topoisomerase IV genes.[106] Increasing resistance to erythromycin and clindamycin now precludes their use as empirical treatment for invasive infection or for intrapartum prophylaxis unless susceptibility is established. Among isolates from patients with invasive disease, resistance rates are approximately 40% for erythromycin and 20% for clindamycin. Most macrolide-resistant strains present a macrolide, lincosamide, and streptogramin B (MLS_B)–resistant phenotype, mainly constitutive, because of *erm* genes.[107] A chromosomally integrated, composite transposon has been defined for *ermB*-type macrolide resistance.[108] Tetracycline resistance has increased to nearly 90%. GBS are uniformly resistant to nalidixic acid, trimethoprim-sulfamethoxazole, metronidazole, and aminoglycosides.

Therapy of 10 days' duration is recommended for the treatment of bacteremia, pneumonia, and pyelonephritis, whereas a 14-day minimal duration is recommended for the treatment of soft tissue infections or meningitis, and a 4-week minimum for the treatment of osteomyelitis, endocarditis, or ventriculitis. In infants, oral therapy is never appropriate. Relapses of infection have occurred in association with both an inadequate dosage and an inadequate duration of therapy. High-dose penicillin therapy does not reliably eliminate mucous membrane infection with GBS, a source that explains some recurrences.

PREVENTION

The impact of maternal intrapartum antibiotic prophylaxis on the incidence of early-onset group B streptococcal disease was first assessed through active, population-based surveillance in selected counties of eight states and reported in 2000.[3] The incidence of early-onset neonatal disease decreased by 65% from 1993 to 1998 and from 1.7 to 0.6 per 1000 live births, and the incidence of invasive disease in pregnant women declined by 21%. A multistate retrospective cohort comparison found that the culture-based approach was 50% more effective than a risk-based approach in preventing early-onset group B streptococcal infection.[109] Guidelines for prevention of perinatal group B streptococcal infection issued by the Centers for Disease Control and Prevention in 2010 specify that lower vaginal and rectal swab screening cultures be performed at 35 to 37 weeks of gestation for all pregnant women, with the exception of patients with documented group B streptococcal bacteriuria during the current pregnancy or with a previous infant with invasive group B streptococcal disease. The indications for intrapartum prophylaxis are shown in Table 201.3. Revision of the guidelines expanded recommendations on laboratory methods for the identification of GBS, clarified that

TABLE 201.3 Indications and Nonindications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset Group B Streptococcal Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy[a]	GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
Positive GBS vaginal-rectal screening culture in late gestation[b] during current pregnancy[a]	Negative vaginal and rectal GBS screening culture in late gestation[b] during the current pregnancy, regardless of intrapartum risk factors
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: • Delivery at <37 wk gestation • Amniotic membrane rupture ≥18 h • Intrapartum temperature ≥100.4°F (≥38.0°C)[c] • Intrapartum NAAT[d] positive for GBS	Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age

[a]Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes.
[b]Optimal timing for prenatal GBS screening is at 35 to 37 weeks' gestation.
[c]If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.
[d]NAAT for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic rupture at ≥18 hours, or temperature ≥100.4°F [≥38.0°C]) is present, then intrapartum antibiotic prophylaxis is indicated.
GBS, Group B streptococci; *NAAT,* nucleic acid amplification test.
From Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. MMWR Recomm Rep. *2010;59(RR-10):1–32.*

a threshold of 10^4 colony-forming units/mL should be used to screen urine for the presence of GBS in women with asymptomatic bacteriuria, and updated algorithms for screening and prophylaxis for women with preterm labor or preterm premature rupture of membranes.[110]

Penicillin G remains the preferred agent for intrapartum prophylaxis because of its relatively narrow spectrum of antimicrobial activity and documented efficacy. The recommendation is to administer 5 million units of penicillin G initially and then 2.5 to 3.0 million units every 4 hours until delivery. Ampicillin (2 g initially, then 1 g every 4 hours) is an acceptable alternative agent, but it has a broader antimicrobial spectrum and can potentially affect the incidence of ampicillin-resistant *Escherichia coli* or other forms of non–group B streptococcal sepsis.[111] Cefazolin (2 g initially, then 1 g every 8 hours until delivery) is recommended for use in penicillin-allergic women who do not have a history of anaphylaxis, angioedema, respiratory distress, or urticaria after administration of a penicillin or cephalosporin. Because of increasing resistance rates of GBS to clindamycin in the United States, susceptibility testing should be performed for antenatal group B streptococcal isolates from penicillin-allergic women at high risk for anaphylaxis. Clindamycin (900 mg intravenously every 8 hours) can be used for prophylaxis only *if* the isolate is susceptible and the result of testing for inducible clindamycin resistance is negative. Vancomycin (1 g every 12 hours until delivery) is the suggested alternative for penicillin-allergic women at high risk for anaphylaxis, but its ability to penetrate into amniotic fluid or to be effective in preventing early-onset disease has not been established.[112]

Several studies have evaluated the potential association between intrapartum antibiotic prophylaxis and the rates of neonatal sepsis caused by other pathogens. The incidence of early-onset *E. coli* cases is slightly decreased, and the proportion of isolates from term infants that are susceptible to ampicillin has not increased. However, for infants born prematurely, especially those weighing less than 1500 g at birth, there has been a significant decrease of *E. coli* isolates causing sepsis that are susceptible to ampicillin. This most likely results from the large proportion of women with preterm labor being treated with antimicrobial agents before sustained labor, but this is an area that requires further studies.

The 2010 guidelines provide a detailed algorithm for management of infants born to mothers who have received intrapartum antibiotic prophylaxis.[110] These advocate a full diagnostic evaluation and empirical treatment for infants with signs of neonatal sepsis and a limited diagnostic evaluation and empirical treatment if intrapartum antibiotics were administered for suspected chorioamnionitis. The guidelines recommend a limited sepsis evaluation with observation for at least 48 hours for infants of less than 37 weeks of gestation or with membrane rupture of at least 18 hours in mothers who did not receive intrapartum prophylaxis with penicillin, ampicillin, or cefazolin for at least 4 hours before delivery. A healthy-appearing infant at term gestation whose mother received 4 or more hours of intrapartum prophylaxis can be discharged home after 24 hours of observation if other discharge criteria have been met and a person able to comply fully with instructions for home observation is available.

Group B Streptococcal Vaccines

Because the risk for invasive group B streptococcal disease in pregnant women and neonates is associated with low concentrations of maternal antibodies to the type-specific capsular polysaccharides of these organisms at delivery, immunization to prevent these infections is desirable. Uncoupled group B streptococcal capsular polysaccharides were poorly immunogenic in healthy adults with low concentrations of capsular-specific antibodies. Capsular polysaccharide-protein conjugate vaccines subsequently were developed. The first, composed of type III polysaccharide covalently linked to tetanus toxoid, was well tolerated and significantly more immunogenic than uncoupled capsular polysaccharide.[113] Additional conjugate vaccines were developed for capsular types Ia, Ib, II, and V polysaccharides. Each of these monovalent conjugate vaccines was well tolerated and immunogenic when administered as a single dose in healthy nonpregnant adults. A type III polysaccharide–tetanus toxoid conjugate vaccine has been administered to healthy women in the third trimester (mean gestation, 31 weeks) of pregnancy.[114] The concentration of capsular polysaccharide–specific IgG was sufficient to provide transplacental antibodies that were functional in vitro through the first 2 months of life for infants born to these women. The concept that two monovalent conjugate vaccines combined can elicit immune responses comparable to those of the monovalent vaccines alone has been proved by the administration to healthy adults of bivalent type II and III group B streptococcal conjugate vaccines.[115]

Administration of a multivalent group B streptococcal polysaccharide–tetanus toxoid conjugate vaccine to women during the last third of pregnancy theoretically could provide capsular type–specific antibodies in sufficient concentrations to passively protect neonates from early- and late-onset disease. Such a multivalent conjugate vaccine tested in a murine model provided protection of pups against lethal infection with multiple group B streptococcal types.[116] This approach to prevention, in contrast to maternal intrapartum antibiotic prophylaxis, offers a method that is simple, cost-effective, and durable and would not promote antimicrobial resistance. Another attribute of maternal GBS immunization is that it would reduce the proportion of US women, currently estimated to be 30%, receiving antibiotics during labor that may be adversely affecting the infant microbiome. The demonstration that type V group B streptococcal polysaccharide–tetanus toxoid conjugate vaccine was well tolerated and immunogenic in healthy older adults also offers promise that immunization could confer protection from invasive infection in at-risk nonpregnant adults, but further studies are needed.[117]

The discovery that surface-associated pili are widely distributed among GBS and that vaccines based on combinations of recombinant pilus components protect mice against lethal challenge with a wide variety of group B streptococcal strains paves the way for design of pilus-based, multivalent vaccines against GBS.[118] Furthermore, pilus islands 1, 2a, and 2b, alone or in combination, were uniformly identified

on more than 200 isolates from infants and adults with invasive group B streptococcal disease, and most were highly surface expressed.[119] Other group B streptococcal surface proteins, including Rib and components of C protein, also offer potential as carriers in conjugate vaccines.[120,121]

Development of multivalent vaccines to prevent group B streptococcal infection has been undertaken by the pharmaceutical industry. In a phase I study that enrolled healthy, nonpregnant women, a single dose of unadjuvanted, preservative-free vaccine consisting of purified capsular polysaccharides of group B streptococcal types Ia, Ib, and III conjugated to cross-reacting material 197 (CRM197) was well tolerated and immunogenic.[122] This trivalent vaccine, when administered during pregnancy in an open-label, phase II, multicenter trial, was less immunogenic in women with HIV infection than it was in those not HIV infected.[123] However, a multivalent conjugate vaccine incorporating six capsular types is needed to prevent most group B streptococcal–associated mortality and morbidity in pregnancy and in fetuses and young infants globally, and possibly to reduce the burden of group B streptococcal disease in adults.

Key References

The complete reference list is available online at Expert Consult.

5. Farley MM. Group B streptococcal disease in nonpregnant adults. *Clin Infect Dis*. 2001;33:556–561.
6. Farley MM, Harvey RC, Stull T, et al. A population-based assessment of invasive disease due to group B streptococcus in non-pregnant adults. *N Engl J Med*. 1993;328:1807–1811.
25. Edwards MS, Rench MA, Palazzi DL, et al. Group B streptococcal colonization and serotype-specific immunity in healthy elderly persons. *Clin Infect Dis*. 2005;40:352–357.
26. Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet*. 2012;379:547–556.
29. Lamagni TL, Keshishian C, Efstratiou A, et al. Emerging trends in the epidemiology of invasive group B streptococcal disease in England and Wales, 1991-2010. *Clin Infect Dis*. 2013;57:682–688.
30. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*. 2008;299:2056–2065.
31. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) Report, Emerging Infections Program Network, Group B Streptococcus, 2016. November 3, 2017. http://www.cdc.gov/abcs/reports-findings/survreports/gbs16.pdf.
32. Skoff TH, Farley MM, Petit S, et al. Increasing burden of invasive group B streptococcal disease in nonpregnant adults, 1990-2007. *Clin Infect Dis*. 2009;49:85–92.
32a. Watkins LKF, McGee L, Schrag SL, et al. Epidemiology of invasive group B streptococcal infections among nonpregnant adults in the United States, 2008-2016. *JAMA Intern Med*. 2019. [Epub ahead of print]
33. Ballard MS, Schönheyder HC, Knudsen JD, et al. The changing epidemiology of group B streptococcus bloodstream infection: a multi-national population-based assessment. *Infect Dis (Lond)*. 2016;48:386–391.
38. Teatero S, Athey TBT, Van Caeseele P, et al. Emergence of serotype IV group B *Streptococcus* adult invasive disease in Manitoba and Saskatchewan, Canada, is driven by clonal sequence type 459 strains. *J Clin Microbiol*. 2015;53:2919–2926.
39. Rosini R, Rinaudo CD, Soriani M, et al. Identification of novel genomic islands coding for antigenic pilus-like structures in *Streptococcus agalactiae*. *Mol Microbiol*. 2006;61:126–141.
41. Maisey HC, Hensler M, Nizet V, et al. Group B streptococcal pilus proteins contribute to adherence to and invasion of brain microvascular endothelial cells. *J Bacteriol*. 2007;189:1464–1467.
44. Pezzicoli A, Santi I, Lauer P, et al. Pilus backbone contributes to group B Streptococcus paracellular translocation through epithelial cells. *J Infect Dis*. 2008;198:890–898.
46. Nizet V, Kim KS, Stins M, et al. Invasion of brain microvascular endothelial cells by group B streptococci. *Infect Immun*. 1997;65:5074–5081.
49. Doran KS, Chang JCW, Benoit VM, et al. Group B streptococcal β-hemolysin/cytolysin promotes invasion of human lung epithelial cells and the release of interleukin-8. *J Infect Dis*. 2002;185:196–203.
51. Takahashi S, Adderson EE, Nagano Y, et al. Identification of a highly encapsulated, genetically related group of invasive type III group B streptococci. *J Infect Dis*. 1998;177:1116–1119.
52. Bellais S, Six A, Fouet A, et al. Capsular switching in group B Streptococcus CC17 hypervirulent clone: a future challenge for polysaccharide vaccine development. *J Infect Dis*. 2012;206:1745–1752.
54. Liu GY, Doran KS, Lawrence T, et al. Sword and shield: linked group B streptococcal beta-hemolysin/cytolysin and carotenoid pigment function to subvert host phagocyte defense. *Proc Natl Acad Sci USA*. 2004;101:14491–14496.
56. Whidbey C, Harrell MI, Burnside K, et al. A hemolytic pigment of group B Streptococcus allows bacterial penetration of human placenta. *J Exp Med*. 2013;210:1265–1281.
59. Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. *N Engl J Med*. 1976;294:753–756.
60. Edwards MS, Rench MA, Rinaudo CD, et al. Immune responses to invasive group B streptococcal disease in adults. *Emerg Infect Dis*. 2016;22:1877–1883.
61. Opal SM, Cross A, Palmer M, et al. Group B streptococcal sepsis in adults and infants: contrasts and comparisons. *Arch Intern Med*. 1988;148:641–645.
62. Gallagher PG, Watanakunakorn C. Group B streptococcal bacteremia in a community teaching hospital. *Am J Med*. 1985;78:795–800.
64. Lerner PI, Gopalakrishna KV, Wolinsky E, et al. Group B streptococcus *(S. agalactiae)* bacteremia in adults: analysis of 32 cases and review of the literature. *Medicine (Baltimore)*. 1977;56:457–473.
65. Schwartz B, Schuchat A, Oxtoby MJ, et al. Invasive group B streptococcal disease in adults: a population-based study in metropolitan Atlanta. *JAMA*. 1991;266:1112–1114.
67. Tyrrell GJ, Senzilet LD, Spika JS, et al. Invasive disease due to group B streptococcal infection in adults: results from a Canadian, population-based, active laboratory surveillance study—1996. *J Infect Dis*. 2000;182:168–173.
68. Jackson LA, Hilsdon R, Farley MM, et al. Risk factors for group B streptococcal disease in adults. *Ann Intern Med*. 1995;123:415–420.
71. Harrison LH, Ali A, Dwyer DM, et al. Relapsing invasive group B streptococcal infection in adults. *Ann Intern Med*. 1995;123:421–427.
74. Bianchi-Jassir F, Seale AC, Kohli-Lynch M, et al. Preterm birth associated with group B Streptococcus maternal colonization worldwide: systematic review and meta-analyses. *Clin Infect Dis*. 2017;65:S133–S142.
75. Seale AC, Blencowe H, Bianchi-Jassir F, et al. Stillbirth with group B Streptococcus disease worldwide: systematic review and meta-analyses. *Clin Infect Dis*. 2017;65:S125–S132.
78. Libster R, Edwards KM, Levent F, et al. Long-term outcomes of group B streptococcal meningitis. *Pediatrics*. 2012;130:e8–e15.
79. Sambola A, Miro JM, Tornos MP, et al. Streptococcus agalactiae infective endocarditis: analysis of 30 cases and review of the literature, 1962-1998. *Clin Infect Dis*. 2002;34:1576–1584.
80. Watanakunakorn C, Habte-Gabr E. Group B streptococcal endocarditis of tricuspid valve. *Chest*. 1991;100:569–571.
84. Sendi P, Christensson B, Uçkay I, et al. Group B streptococcus in prosthetic hip and knee joint-associated infections. *J Hosp Infect*. 2011;79:64–69.
85. García-Lechuz JM, Bachiller P, Vasallo FJ, et al. Group B streptococcal osteomyelitis in adults. *Medicine (Baltimore)*. 1999;78:191–199.
86. Kernéis S, Plainvert C, Barnier J-P, et al. Clinical and microbiological features associated with group B Streptococcus bone and joint infections, France 2004-2014. *Eur J Clin Micribiol Infect Dis*. 2017;36:1679–1684.
89. Tang WM, Ho PL, Yau WP, et al. Report of 2 fatal cases of adult necrotizing fasciitis and toxic shock syndrome caused by Streptococcus agalactiae. *Clin Infect Dis*. 2000;31:e15–e17.
90. Domingo P, Barquet N, Alvarez M, et al. Group B streptococcal meningitis in adults: report of twelve cases and review. *Clin Infect Dis*. 1997;25:1180–1187.
103. Davies HD, Miller MA, Faro S, et al. Multicenter study of a rapid molecular-based assay for the diagnosis of group B Streptococcus colonization in pregnant women. *Clin Infect Dis*. 2004;39:1129–1135.
104. Kimura K, Suzuki S, Wachino J, et al. First molecular characterization of group B streptococci with reduced penicillin susceptibility. *Antimicrob Agents Chemother*. 2008;52:2890–2897.
105. Park C, Nichols M, Schraq SJ. Two cases of invasive vancomycin-resistant group B streptococcus infection. *N Engl J Med*. 2014;370:885–886.
106. Wehbeh W, Rojas-Diaz R, Li X, et al. Fluoroquinolone-resistant Streptococcus agalactiae: epidemiology and mechanism of resistance. *Antimicrob Agents Chemother*. 2005;49:2495–2497.
109. Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med*. 2002;347:233–239.
110. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR–10):1–32.
113. Kasper DL, Paoletti LC, Wessels MR, et al. Immune response to type III group B streptococcal polysaccharide–tetanus toxoid conjugate vaccine. *J Clin Invest*. 1996;98:2308–2314.
114. Baker CJ, Rench MA, McInnes P. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. *Vaccine*. 2003;21:3468–3472.
115. Baker CJ, Rench MA, Fernandez M, et al. Safety and immunogenicity of a bivalent group B streptococcal conjugate vaccine for serotypes II and III. *J Infect Dis*. 2003;188:66–73.
117. Palazzi DL, Rench MA, Edwards MS, et al. Use of type V group B streptococcal conjugate vaccine in adults 65-85 years old. *J Infect Dis*. 2004;190:558–564.
119. Margarit I, Rinaudo CD, Galeotti CL, et al. Preventing bacterial infections with pilus-based vaccines: the group B Streptococcus paradigm. *J Infect Dis*. 2009;199:108–115.
122. Leroux-Roels G, Maes C, Willekens J, et al. A randomized, observer-blind Phase Ib study to identify formulations and vaccine schedules of a trivalent group B Streptococcus vaccine for use in non-pregnant and pregnant women. *Vaccine*. 2016;34:1786–1791.

References

1. Fry RM. Fatal infections by haemolytic streptococcus group B. *Lancet*. 1938;1:199–201.
2. Eickhoff TC, Klein JO, Daly AL, et al. Neonatal sepsis and other infections due to group B beta-hemolytic streptococci. *N Engl J Med*. 1964;271:1221–1228.
3. Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med*. 2000;342:15–20.
4. Muñoz P, Llancaqueo A, Rodriguez-Creixems M, et al. Group B streptococcus bacteremia in nonpregnant adults. *Arch Intern Med*. 1997;157:213–216.
5. Farley MM. Group B streptococcal disease in nonpregnant adults. *Clin Infect Dis*. 2001;33:556–561.
6. Farley MM, Harvey RC, Stull T, et al. A population-based assessment of invasive disease due to group B streptococcus in non-pregnant adults. *N Engl J Med*. 1993;328:1807–1811.
7. Henning KJ, Hall EL, Dwyer DM, et al. Invasive group B streptococcal disease in Maryland nursing home residents. *J Infect Dis*. 2001;183:1138–1142.
8. Glaser P, Rusniok C, Buchrieser C, et al. Genome sequence of *Streptococcus agalactiae*, a pathogen causing invasive neonatal disease. *Mol Microbiol*. 2002;45:1499–1513.
9. Tettelin H, Masignani V, Cieslewicz MJ, et al. Complete genome sequence and comparative genomic analysis of an emerging human pathogen, serotype V *Streptococcus agalactiae*. *Proc Natl Acad Sci USA*. 2002;99:12391–12396.
10. Lancefield RC. A serological differentiation of specific types of bovine hemolytic streptococci (group B). *J Exp Med*. 1934;59:441–458.
11. Wilkinson HW, Eagon RG. Type-specific antigens of group B type Ic streptococci. *Infect Immun*. 1971;4:596–604.
12. Henrichsen J, Ferrieri P, Jelinkova J, et al. Nomenclature of antigens of group B streptococci. *Int J Syst Bacteriol*. 1984;34:500.
13. Ferrieri P, Flores AE. Surface protein expression in group B streptococcal invasive isolates. *Adv Exp Med Biol*. 1997;418:635–637.
14. Lancefield RC, McCarty M, Everly WN. Multiple mouse-protective antibodies directed against group B streptococci. Special reference to antibodies effective against protein antigens. *J Exp Med*. 1975;142:165–179.
15. Stålhammar-Carlemalm M, Stenberg L, Lindahl G. Protein Rib: a novel group B streptococcal cell surface protein that confers protective immunity and is expressed by most strains causing invasive infections. *J Exp Med*. 1993;177:1593–1603.
16. Madoff LC, Michel JL, Gong EW, et al. Protection of neonatal mice from group B streptococcal infection by maternal immunization with beta C protein. *Infect Immun*. 1992;60:4989–4994.
17. Sørensen UBS, Poulsen K, Ghezzo C, et al. Emergence and global dissemination of host-specific *Streptococcus agalactiae* clones. *MBio*. 2010;1:e00178-10.
18. Imperi M, Pataracchia M, Alfarone G, et al. A multiplex PCR assay for the direct identification of the capsular type (Ia to IX) of *Streptococcus agalactiae*. *J Microbiol Meth*. 2010;80:212–214.
19. Sheppard AE, Vaughn A, Jones N, et al. Capsular typing method for *Streptococcus agalactiae* using whole genome sequence data. *J Clin Microbiol*. 2016;54:1388–1390.
20. Quentin R, Huet H, Wang F-S, et al. Characterization of *Streptococcus agalactiae* strains by multilocus enzyme genotype and serotype: identification of multiple virulent clone families that cause invasive neonatal disease. *J Clin Microbiol*. 1995;33:2576–2581.
21. Lartigue MF, Kostrzewa M, Salloum M, et al. Rapid detection of "highly virulent" group B *Streptococcus* ST-17 and emerging ST-1 clones by MALDI-TOF mass spectrometry. *J Microbiol Methods*. 2011;86:262–265.
22. Manning SD, Tallman P, Baker CJ, et al. Determinants of cocolonization with group B streptococcus among heterosexual college couples. *Epidemiology*. 2002;13:533–539.
23. Meyn LA, Krohn MA, Hillier SL. Rectal colonization by group B *Streptococcus* as a predictor of vaginal colonization. *Am J Obstet Gynecol*. 2009;201:76.e1-76.e7.
24. Manning SD, Lewis MA, Springman AC, et al. Genotypic diversity and serotype distribution of group B *Streptococcus* isolated from women before and after delivery. *Clin Infect Dis*. 2008;46:1829–1837.
25. Edwards MS, Rench MA, Palazzi DL, et al. Group B streptococcal colonization and serotype-specific immunity in healthy elderly persons. *Clin Infect Dis*. 2005;40:352–357.
26. Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet*. 2012;379:547–556.
27. Dagnew AF, Cunnington MC, Dube Q, et al. Variation in reported neonatal group B streptococcal disease incidence in developing countries. *Clin Infect Dis*. 2012;55:91–102.
28. Crespo-Ortiz Mdel P, Castañeda-Ramirez CR, et al. Emerging trends in invasive and noninvasive *Streptococcus agalactiae* in a Latin American hospital: a 17-year study. *BMC Infect Dis*. 2014;14:428.
29. Lamagni TL, Keshishian C, Efstratiou A, et al. Emerging trends in the epidemiology of invasive group B streptococcal disease in England and Wales, 1991-2010. *Clin Infect Dis*. 2013;57:682–688.
30. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*. 2008;299:2056–2065.
31. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) Report, Emerging Infections Program Network, Group B *Streptococcus*, 2016. November 3, 2017. http://www.cdc.gov/abcs/reports-findings/survreports/gbs16.pdf.
32. Skoff TH, Farley MM, Petit S, et al. Increasing burden of invasive group B streptococcal disease in nonpregnant adults, 1990-2007. *Clin Infect Dis*. 2009;49:85–92.

32a. Watkins LKF, McGee L, Schrag SL, et al. Epidemiology of invasive group B streptococcal infections among nonpregnant adults in the United States, 2008-2016. *JAMA Intern Med*. 2019. [Epub ahead of print]

33. Ballard MS, Schönheyder HC, Knudsen JD, et al. The changing epidemiology of group B streptococcus bloodstream infection: a multi-national population-based assessment. *Infect Dis (Lond)*. 2016;48:386–391.
34. Tazi A, Morand PC, Réglier-Poupet H, et al. Invasive group B streptococcal infections in adults, France (2007-2010). *Clin Microbiol Infect*. 2011;17:1587–1589.
35. Dutra VG, Alves VM, Olendzki AN, et al. *Streptococcus agalactiae* in Brazil: serotype distribution, virulence determinants and antimicrobial susceptibility. *BMC Infect Dis*. 2014;14:323.
36. Lachenauer C, Kasper DL, Shimada J, et al. Serotypes VI and VIII predominate among group B streptococci isolated from pregnant Japanese women. *J Infect Dis*. 1999;174:1030–1033.
37. Florindo C, Damiao V, Silvestre I, et al. Epidemiological surveillance of colonizing group B *Streptococcus* epidemiology in Lisbon and Tagus Valley regions, Portugal (2005 to 2012): emergence of a new epidemic type IV/clonal complex 17 clone. *Euro Surveill*. 2014;19:pii:20825.
38. Teatero S, Athey TBT, Van Caeseele P, et al. Emergence of serotype IV group B *Streptococcus* adult invasive disease in Manitoba and Saskatchewan, Canada, is driven by clonal sequence type 459 strains. *J Clin Microbiol*. 2015;53:2919–2926.
39. Rosini R, Rinaudo CD, Soriani M, et al. Identification of novel genomic islands coding for antigenic pilus-like structures in *Streptococcus agalactiae*. *Mol Microbiol*. 2006;61:126–141.
40. Bolduc GR, Baron MJ, Gravekamp C, et al. The alpha C protein mediates internalization of group B *Streptococcus* within human cervical epithelial cells. *Cell Microbiol*. 2002;4:751–758.
41. Maisey HC, Hensler M, Nizet V, et al. Group B streptococcal pilus proteins contribute to adherence to and invasion of brain microvascular endothelial cells. *J Bacteriol*. 2007;189:1464–1467.
42. Schubert A, Zakikhany K, Pietrocola G, et al. The fibrinogen receptor FbsA promotes adherence of *Streptococcus agalactiae* to human cells. *Infect Immun*. 2004;72:6197–6205.
43. Soriani M, Santi I, Taddei A, et al. Group B *Streptococcus* crosses human epithelial cells by a paracellular route. *J Infect Dis*. 2006;193:241–250.
44. Pezzicoli A, Santi I, Lauer P, et al. Pilus backbone contributes to group B *Streptococcus* paracellular translocation through epithelial cells. *J Infect Dis*. 2008;198:890–898.
45. Gutekunst H, Eikmanns BJ, Reinscheid DJ. The novel fibrogen-binding protein FbsB promotes *Streptococcus agalactiae* invasion into epithelial cells. *Infect Immun*. 2004;72:3495–3504.
46. Nizet V, Kim KS, Stins M, et al. Invasion of brain microvascular endothelial cells by group B streptococci. *Infect Immun*. 1997;65:5074–5081.
47. Baron MJ, Filman DJ, Prophete GA, et al. Identification of a glycosaminoglycan binding region of the alpha C protein that mediates entry of group B streptococci into host cells. *J Biol Chem*. 2007;282:10526–10536.
48. Doran KS, Engelson EJ, Khosravi A, et al. Blood-brain barrier invasion by group B *Streptococcus* depends upon proper cell-surface anchoring of lipoteichoic acid. *J Clin Invest*. 2005;115:2499–2507.
49. Doran KS, Chang JCW, Benoit VM, et al. Group B streptococcal β-hemolysin/cytolysin promotes invasion of human lung epithelial cells and the release of interleukin-8. *J Infect Dis*. 2002;185:196–203.
50. Gibson RL, Nizet V, Rubens CE. Group B streptococcal beta-hemolysin promotes injury of lung microvascular endothelial cells. *Pediatr Res*. 1999;45(5 Pt 1):626–634.
51. Takahashi S, Adderson EE, Nagano Y, et al. Identification of a highly encapsulated, genetically related group of invasive type III group B streptococci. *J Infect Dis*. 1998;177:1116–1119.
52. Bellais S, Six A, Fouet A, et al. Capsular switching in group B *Streptococcus* CC17 hypervirulent clone: a future challenge for polysaccharide vaccine development. *J Infect Dis*. 2012;206:1745–1752.
53. Granlund M, Oberg L, Sellin M, et al. Identification of a novel insertion element, IS*1548*, in group B streptococci, predominantly in strains causing endocarditis. *J Infect Dis*. 1998;177:967–976.
54. Liu GY, Doran KS, Lawrence T, et al. Sword and shield: linked group B streptococcal beta-hemolysin/cytolysin and carotenoid pigment function to subvert host phagocyte defense. *Proc Natl Acad Sci USA*. 2004;101:14491–14496.
55. Hensler ME, Miyamoto S, Nizet V. Group B streptococcal β-hemolysin/cytolysin directly impairs cardiomyocyte viability and function. *PLoS ONE*. 2008;3:e2446–e2452.
56. Whidbey C, Harrell MI, Burnside K, et al. A hemolytic pigment of group B *Streptococcus* allows bacterial penetration of human placenta. *J Exp Med*. 2013;210:1265–1281.
57. Areschoug T, Stalhammar-Carlemalm M, Karlsson I, et al. Streptococcal beta protein has separate binding sites for human factor H and IgA-Fc. *J Biol Chem*. 2002;277:12642–12648.
58. Harris TO, Shelver DW, Bohnsack JF, et al. A novel streptococcal surface protease promotes virulence, resistance to opsonophagocytosis, and cleavage of human fibrinogen. *J Clin Invest*. 2003;111:61–70.
59. Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. *N Engl J Med*. 1976;294:753–756.
60. Edwards MS, Rench MA, Rinaudo CD, et al. Immune responses to invasive group B streptococcal disease in adults. *Emerg Infect Dis*. 2016;22:1877–1883.
61. Opal SM, Cross A, Palmer M, et al. Group B streptococcal sepsis in adults and infants: contrasts and comparisons. *Arch Intern Med*. 1988;148:641–645.
62. Gallagher PG, Watanakunakorn C. Group B streptococcal bacteremia in a community teaching hospital. *Am J Med*. 1985;78:795–800.
63. Verghese A, Mireault K, Arbeit RD. Group B streptococcal bacteremia in men. *Rev Infect Dis*. 1986;8:912–917.
64. Lerner PI, Gopalakrishna KV, Wolinsky E, et al. Group B streptococcus *(S. agalactiae)* bacteremia in adults: analysis of 32 cases and review of the literature. *Medicine (Baltimore)*. 1977;56:457–473.
65. Schwartz B, Schuchat A, Oxtoby MJ, et al. Invasive group B streptococcal disease in adults: a population-based study in metropolitan Atlanta. *JAMA*. 1991;266:1112–1114.
66. Kothari NJ, Morin CA, Glennen A, et al. Invasive group B streptococcal disease in the elderly, Minnesota, USA, 2003-2007. *Emerg Infect Dis*. 2009;15:1279–1281.
67. Tyrrell GJ, Senzilet LD, Spika JS, et al. Invasive disease due to group B streptococcal infection in adults: results from a Canadian, population-based, active laboratory surveillance study—1996. *J Infect Dis*. 2000;182:168–173.
68. Jackson LA, Hilsdon R, Farley MM, et al. Risk factors for group B streptococcal disease in adults. *Ann Intern Med*. 1995;123:415–420.
69. Blancas D, Santin M, Olmo M, et al. Group B streptococcal disease in nonpregnant adults: incidence, clinical characteristics, and outcome. *Eur J Clin Microbiol Infect Dis*. 2004;23:168–173.
70. Kaseman JA, Myers NM, Miracle JE, et al. Group B streptococcal bacteremia in adults in the 21st century. *Infect Dis Clin Pract*. 2013;21:105–110.
71. Harrison LH, Ali A, Dwyer DM, et al. Relapsing invasive group B streptococcal infection in adults. *Ann Intern Med*. 1995;123:421–427.
72. Gibbs RS, Roberts DJ. Case records of the Massachusetts General Hospital. Case 27-2007: a 30-year-old pregnant woman with intrauterine fetal death. *N Engl J Med*. 2007;357:918–925.
73. Boyle D, Smith JR. Group B streptococcal vulvovaginitis. *J R Soc Med*. 1997;90:298–299.
74. Bianchi-Jassir F, Seale AC, Kohli-Lynch M, et al. Preterm birth associated with group B *Streptococcus* maternal colonization worldwide: systematic review and meta-analyses. *Clin Infect Dis*. 2017;65:S133–S142.

75. Seale AC, Blencowe H, Bianchi-Jassir F, et al. Stillbirth with group B *Streptococcus* disease worldwide: systematic review and meta-analyses. *Clin Infect Dis*. 2017;65: S125–S132.
76. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics*. 2005;115:1240–1246.
77. Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease. A multistate, population-based analysis. *Pediatr Infect Dis J*. 2008;27:1057–1064.
78. Libster R, Edwards KM, Levent F, et al. Long-term outcomes of group B streptococcal meningitis. *Pediatrics*. 2012;130:e8–e15.
79. Sambola A, Miro JM, Tornos MP, et al. *Streptococcus agalactiae* infective endocarditis: analysis of 30 cases and review of the literature, 1962-1998. *Clin Infect Dis*. 2002;34:1576–1584.
80. Watanakunakorn C, Habte-Gabr E. Group B streptococcal endocarditis of tricuspid valve. *Chest*. 1991;100:569–571.
81. Ivanova Georgieva R, Garcia López MV, Ruiz-Morales J, et al. *Streptococcus agalactiae* left-sided endocarditis. Analysis of 27 cases from a multicentric cohort. *J Infect*. 2010;61:54–59.
82. Pringle SD, McCartney AC, Marshall DA, et al. Infective endocarditis caused by *Streptococcus agalactiae*. Report of a case and review of the literature. *Int J Cardiol*. 1989;24:179–183.
83. Nolla JM, Gómez-Vaquero C, Corbella X, et al. Group B streptococcus *(Streptococcus agalactiae)* pyogenic arthritis in nonpregnant adults. *Medicine (Baltimore)*. 2003;82: 119–128.
84. Sendi P, Christensson B, Uçkay I, et al. Group B streptococcus in prosthetic hip and knee joint-associated infections. *J Hosp Infect*. 2011;79:64–69.
85. García-Lechuz JM, Bachiller P, Vasallo FJ, et al. Group B streptococcal osteomyelitis in adults. *Medicine (Baltimore)*. 1999;78:191–199.
86. Kernéis S, Plainvert C, Barnier J-P, et al. Clinical and microbiological features associated with group B *Streptococcus* bone and joint infections, France 2004-2014. *Eur J Clin Micribiol Infect Dis*. 2017;36: 1679–1684.
87. Sendi P, Graber P, Johansson L, et al. *Streptococcus agalactiae* in relapsing cellulitis. *Clin Infect Dis*. 2007;44:1141–1142.
88. Riefler J 3rd, Molavi A, Schwartz D, et al. Necrotizing fasciitis in adults due to group B streptococcus. *Arch Intern Med*. 1988;148:727–729.
89. Tang WM, Ho PL, Yau WP, et al. Report of 2 fatal cases of adult necrotizing fasciitis and toxic shock syndrome caused by *Streptococcus agalactiae*. *Clin Infect Dis*. 2000;31:e15–e17.
90. Domingo P, Barquet N, Alvarez M, et al. Group B streptococcal meningitis in adults: report of twelve cases and review. *Clin Infect Dis*. 1997;25:1180–1187.
91. Guerin JM, Leibinger F, Mofredj A, et al. Streptococcus B meningitis in post-partum. *J Infect*. 1997;34:151–153.
92. Ulett KB, Benjamin WH Jr, Zhuo F, et al. Diversity of group B *Streptococcus* serotypes causing urinary tract infection in adults. *J Clin Microbiol*. 2009;47:2055–2060.
93. Ormerod LD, Paton BG. Severe group B streptococcal eye infections in adults. *J Infect*. 1989;18:29–34.
94. Weiss RL, Matsen JM. Group B streptococcal breast abscess. *Arch Pathol Lab Med*. 1987;111:74–75.
95. Kane JM, Jackson K, Conway JH. Maternal postpartum group B beta-hemolytic streptococcus ventriculoperitoneal shunt infection. *Arch Gynecol Obstet*. 2004;269:139–141.
96. Oyanguren B, Esteban L, Guillán M, et al. Central nervous system involvement in adult patients with invasive infection caused by *Streptococcus agalactiae*. *Neurología*. 2015;30:158–162.
97. Thawait SK, Akay A, Jhirad RH, et al. Group B *Streptococcus* mycotic aneurysm of the abdominal aorta: report of a case and review of the literature. *Yale J Biol Med*. 2012;85:97.
98. Crum-Cianflone NF. An unusual case of a large, sporadic intra-abdominal abscess due to group B *Streptococcus* and a review of the literature. *Infection*. 2015;43:223–227.
99. Baddour LM, Cox JW Jr. Group B streptococcal infection of a pacemaker wire following sigmoidoscopy. *Clin Infect Dis*. 1992;15:1069.
100. Al Akhrass F, Abdallah L, Berger S, et al. *Streptococcus agalactiae* toxic shock-like syndrome: two case reports and review of the literature. *Medicine (Baltimore)*. 2013;92:10–14.
101. Bergeron MG, Ke D, Ménard C, et al. Rapid detection of group B streptococci in pregnant women at delivery. *N Engl J Med*. 2000;343:175–179.
102. Edwards RK, Novak-Weekley SM, Koty PP, et al. Rapid group B streptococci screening using a real-time polymerase chain reaction assay. *Obstet Gynecol*. 2008;111:1335–1341.
103. Davies HD, Miller MA, Faro S, et al. Multicenter study of a rapid molecular-based assay for the diagnosis of group B *Streptococcus* colonization in pregnant women. *Clin Infect Dis*. 2004;39:1129–1135.
104. Kimura K, Suzuki S, Wachino J, et al. First molecular characterization of group B streptococci with reduced penicillin susceptibility. *Antimicrob Agents Chemother*. 2008;52:2890–2897.
105. Park C, Nichols M, Schraq SJ. Two cases of invasive vancomycin-resistant group B streptococcus infection. *N Engl J Med*. 2014;370:885–886.
106. Wehbeh W, Rojas-Diaz R, Li X, et al. Fluoroquinolone-resistant *Streptococcus agalactiae*: epidemiology and mechanism of resistance. *Antimicrob Agents Chemother*. 2005;49:2495–2497.
107. Aracil B, Miñambres M, Oteo J, et al. Susceptibility of strains of *Streptococcus agalactiae* to macrolides and lincosamides, phenotype patterns and resistance genes. *Clin Microbiol Infect*. 2002;8:745–748.
108. Puopolo KM, Klinzing DC, Lin MP, et al. A composite transposon associated with erythromycin and clindamycin resistance in group B *Streptococcus*. *J Med Microbiol*. 2007;56(Pt 7):947–955.
109. Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med*. 2002;347:233–239.
110. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR–10):1–32.
111. Schrag SS, Stoll BJ. Early-onset neonatal sepsis in the era of widespread intrapartum chemoprophylaxis. *Pediatr Infect Dis J*. 2006;25:939–940.
112. Matteson KA, Lievense SP, Catanzaro B, et al. Intrapartum group B streptococci prophylaxis in patients reporting a penicillin allergy. *Obstet Gynecol*. 2008;111(2 Pt 1):356–364.
113. Kasper DL, Paoletti LC, Wessels MR, et al. Immune response to type III group B streptococcal polysaccharide–tetanus toxoid conjugate vaccine. *J Clin Invest*. 1996;98:2308–2314.
114. Baker CJ, Rench MA, McInnes P. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. *Vaccine*. 2003;21:3468–3472.
115. Baker CJ, Rench MA, Fernandez M, et al. Safety and immunogenicity of a bivalent group B streptococcal conjugate vaccine for serotypes II and III. *J Infect Dis*. 2003;188:66–73.
116. Paoletti LC, Wessels MR, Rodewald AK, et al. Neonatal mouse protection against infection with multiple group B streptococcal (GBS) serotypes by maternal immunization with a tetravalent GBS polysaccharide-tetanus toxoid conjugate vaccine. *Infect Immun*. 1994;62:3236–3243.
117. Palazzi DL, Rench MA, Edwards MS, et al. Use of type V group B streptococcal conjugate vaccine in adults 65-85 years old. *J Infect Dis*. 2004;190:558–564.
118. Buccato S, Maione D, Rinaudo CD, et al. Use of *Lactococcus lactis* expressing pili from group B *Streptococcus* as a broad-coverage vaccine against streptococcal disease. *J Infect Dis*. 2006;194:331–340.
119. Margarit I, Rinaudo CD, Galeotti CL, et al. Preventing bacterial infections with pilus-based vaccines: the group B *Streptococcus* paradigm. *J Infect Dis*. 2009;199:108–115.
120. Yang H-H, Madoff LC, Guttormsen H-K, et al. Recombinant group B *Streptococcus* beta C protein and a variant with the deletion of its immunoglobulin A-binding site are protective mouse maternal vaccines and effective carriers in conjugate vaccines. *Infect Immun*. 2007;75:3455–3461.
121. Larsson C, Lindroth M, Nordin P, et al. Association between low concentrations of antibodies to protein α and Rib and invasive neonatal group B streptococcal infection. *Arch Dis Child Fetal Neonatal Ed*. 2006;91:F403–F408.
122. Leroux-Roels G, Maes C, Willekens J, et al. A randomized, observer-blind Phase Ib study to identify formulations and vaccine schedules of a trivalent group B *Streptococcus* vaccine for use in non-pregnant and pregnant women. *Vaccine*. 2016;34:1786–1791.
123. Heyderman RS, Madhi SA, French N, et al. Group B *Streptococcus* vaccination in pregnant women with or without HIV in Africa: a non-randomized phase 2, open-label, multicentre trial. *Lancet Inf Dis*. 2016;16:546–555.

202 Viridans Streptococci, Nutritionally Variant Streptococci, and Groups C and G Streptococci

Cheston B. Cunha

SHORT VIEW SUMMARY

Overview
- The habitat, epidemiology, microbiology, clinical manifestations, and therapy of the viridans streptococci, including the *Streptococcus anginosus* group, nutritionally variant streptococci (NVS), and groups C and G streptococci, are discussed in this chapter.

Habitat
- The viridans streptococci are part of the normal microbiota of the oropharynx, skin, and gastrointestinal (GI) tract. These organisms lack the virulence factors of β-hemolytic streptococci and are opportunistic pathogens in specific clinical settings, for instance, damaged heart valves (subacute endocarditis [SBE]) and severe neutropenia (bacteremia).

Microbiology
- Most viridans streptococci demonstrate α- or γ-hemolysis and are not typeable by Lancefield antisera. These organisms are gram-positive cocci arranged in chains and are facultatively anaerobic. Viridans streptococci are catalase and coagulase negative. The NVS require thiol compounds for growth. Groups C and G streptococci may demonstrate β-hemolysis resembling that of group A streptococci (GAS).

Virulence
- Viridans streptococci are primarily colonizers of the oral and GI mucosa. Strains produce varying amounts of capsular polysaccharide (dextran) essential for adherence and colonization. Strains with abundant capsule production are the most likely strains to cause SBE. Capsular polysaccharide also inhibits phagocytosis. Most viridans streptococci are not organisms that induce a pyogenic response. Abscesses formation is a characteristic of the *S. anginosus* group of viridans streptococci.

Clinical Manifestations
- The most frequent infection caused by the viridans streptococci, including NVS, is native valve SBE. Abscesses of teeth, brain, liver, and abdomen are caused by the *S. anginosus* group of viridans staphylococci, but these organisms rarely cause SBE. Groups C and G streptococci most often cause pharyngitis or cellulitis in the elderly, diabetic persons, cirrhotic persons, or those with malignancy.

Diagnosis
- The diagnosis of viridans streptococcal SBE is based on demonstrating a high-grade continuous bacteremia and a valvular vegetation. With suspected SBE due to NVS, blood media are supplemented with vitamin B_6 and subcultured on chocolate agar. In *S. anginosus* group abscesses, diagnosis is by culture of the organism. Acute pharyngitis due to groups C and G streptococci resembles GAS pharyngitis and is diagnosed by throat culture. Cellulitis due to group C or G streptococci is indistinguishable from GAS or group B streptococci cellulitis unless the organism is identified in positive blood cultures.

Antimicrobial Therapy
- The viridans streptococci remain highly susceptible to penicillin and β-lactams. Resistance is minimal and, if present, is a "relative resistance" responsive to high-dose penicillin and β-lactams. The NVS are relatively more penicillin resistant than other viridans streptococci. Like staphylococci, viridans streptococci may demonstrate antibiotic "tolerance." The main therapeutic challenge in treating viridans streptococcal SBE is not antibiotic resistance to penicillin or β-lactams, but it is related to antibiotic penetration of valvular vegetations.

OVERVIEW

The viridans group streptococci (VGS) are a diverse group of organisms and are the predominant microbiota in the oropharynx and gastrointestinal (GI) tract. The viridans streptococci cause a significant percentage of all cases of infective endocarditis (IE). *Streptococcus mutans* is responsible for dental caries. Several typing schemes for the VGS have been proposed. There are at least 30 recognized species of VGS, which are classified into six major groups: *S. mutans* group, *Streptococcus salivarius* group, *Streptococcus mitis* group, *Streptococcus sanguinis* group, *Streptococcus anginosus* group, and *Streptococcus bovis* group.[1] The *S. anginosus* group has been the one that is most difficult to classify because all isolates are not uniformly α-hemolytic; some are γ-hemolytic or β-hemolytic. VGS usually do not react with Lancefield grouping antisera, exceptions being some strains of *S. anginosus*, which may react with Lancefield A, C, F, or G antisera. *S. bovis*, a nonenterococcal group D streptococcus, has some characteristics of the enterococci and reacts with Lancefield D antisera.

VGS are catalase-negative, gram-positive cocci in chains, which are leucine aminopeptidase positive, pyrrolidonyl arylamidase (PYR) negative, and do not grow in bile esculin agar or 6.5% sodium chloride (NaCl) broth. The differentiation of *Streptococcus pneumoniae* from VGS is by optochin (ethylhydrocupreine hydrochloride) susceptibility and bile solubility.[1] Because of its major role in disease, Chapter 199 is devoted to *S. pneumoniae*.

Viridans streptococci are so named for their green discoloration surrounding colonies, (α-hemolysis) on blood agar, but some species produce no greenish discoloration (γ-hemolysis). Viridans streptococci are common colonizers of the oropharynx, GI tract, and skin. Colonizing strains of viridans streptococci produce abundant capsular material that facilitates adherence to epithelial cells. Colonization of mucosal surfaces, for instance, the oropharynx by viridans streptococci, is protective against colonization by other organisms, such as aerobic gram-negative bacilli.

With the exception of *S. pneumoniae*, *Streptococcus mitis*, and the *S. anginosus* group, viridans streptococci are relatively avirulent and are opportunistic pathogens usually requiring damaged tissue, such as heart valves, or impaired neutrophil function, such as chemotherapy-induced neutropenia. Unlike the other viridans streptococci, the *S. anginosus* group is associated with abscess formation. Streptococci are gram-positive cocci and are facultatively anaerobic or microaerophilic, catalase negative, and arranged in pairs or chains. With the exception of group A streptococci (GAS), streptococcal virulence is inversely related to chain length, for instance, *S. pneumoniae* (diplococci) are more virulent than viridans streptococci (long chains). Most streptococci may be classified on the basis of their pattern of hemolysis on blood agar, Lancefield antigens, and biochemical reactions.

Streptococci are nutritionally fastidious, grow best in blood-supplemented media, and produce lactic acid without gas from glucose.

Lancefield groups A, B, C, and G streptococci are β-hemolytic. α-Hemolytic streptococci include numerous species, but the most important are *S. pneumoniae* and *S. mitis*. Viridans streptococci are a diverse group of streptococci usually demonstrating α-hemolysis and generally possessing no Lancefield cell wall antigens. They are collectively referred to as VGS.

Viridans streptococci consists of groups of organisms, for instance, the *S. mitis* group, *S. mutans* group, *S. salivarius* group, and *S. sanguinis* group (Tables 202.1 and 202.2). Each viridans group is associated with particular infections of oral origin. *S. mutans* is associated with dental caries and pleuropulmonary infection. *S. mutans* and *S. sanguinis* are frequent causes of subacute endocarditis (SBE).

The *S. anginosus* group differs from other viridans streptococci in its ability to cause invasive pyogenic infections, such as abscesses (brain, dental, lung, liver, abdomen). Unlike the other viridans streptococci, the *S. sanguinis* group rarely causes SBE.[2]

Another distinctive group of viridans streptococci are the nutritionally variant (deficient) streptococci (NVS), also referred to as pyridoxal (vitamin B_6)–dependent or "satelliting streptococci." The NVS consist of two genera: *Abiotrophia* sp. and *Granulicatella* spp. SBE is the classic infection caused by these NVS (*Abiotrophia* sp. and *Granulicatella* spp.) and is often clinically more severe than infection caused by other viridans streptococci.[3] Although consisting of four species in two genera, the term *NVS* will be used in this chapter for historical reasons, and this term is a reminder of their fastidious nutritional requirements.

MICROBIOLOGY

Viridans Streptococci

Viridans streptococci are gram-positive cocci arranged in pairs and chains and are facultative anaerobes, but some strains are microaerophilic. As a group viridans streptococci are fastidious organisms and grow best on blood agar but form small, raised colonies. They are nonmotile and nonspore formers. The viridans streptococci produce lactic acid, but not gas, from glucose. Colony size and characteristics vary by species.[4]

Greenish discoloration surrounding viridans streptococcal colonies ("viridans" from the Latin *virdis,* meaning "green") results in a greenish discoloration on blood agar that is due to partial red blood cell destruction. In general, the type of hemolysis distinguishes the viridans streptococci, but some strains may demonstrate γ-hemolysis or β-hemolysis. The intensity of α-hemolysis, that is, the intensity of greenish discoloration varies with the medium and viridans streptococcal species. Streptococcal colonies often glisten. After 24 hours of incubation, β-hemolytic streptococci (GAS, group C streptococci [GCS], and group G streptococci [GGS]) form large colonies (>0.5 mm in diameter); β-hemolytic small colonies suggest the *S. anginosus* group. These small *S. anginosus* (<0.5 mm in diameter) "pinpoint colonies" have honey or caramel odor. Group B β-hemolytic streptococcal colonies are larger and demonstrate less intense β-hemolysis (smaller zone) than other β-hemolytic streptococci. Colonies of viridans streptococci demonstrate α-hemolysis and have a "domed" appearance, in contrast to the flat colonies of other streptococci. The α-hemolytic colonies of *S. pneumoniae*

TABLE 202.1 Viridans Streptococci Group

	MOST COMMON HUMAN ISOLATES	OTHER GROUP SPECIES
***S. mitis* Group**		
S. cristatus		*S. cristatus*
S. infantis		*S. infantis*
S. mitis	*S. mitis*	
S. oralis	*S. oralis*	
S. peroris		*S. peroris*
S. tigurinus		*S. tigurinus*
***S. mutans* Group**		
S. cricetus		*S. cricetus*
S. downei		*S. downei*
S. ferus		*S. ferus*
S. hyobvaginalis		*S. hyobvaginalis*
S. macacae		*S. macacae*
S. mutans	*S. mutans*	
S. ratti		*S. ratti*
***S. salivarius* Group**		
S. alactolyticus		*S. alactolyticus*
S. hyointestinalis		*S. hyointestinalis*
S. infantarius		*S. infantarius*
S. salivarius	*S. salivarius*	
S. thermophilus		*S. thermophilus*
S. vestibularis	*S. vestibularis*	
***S. sanguinis* Group**		
S. gordonii	*S. gordonii*	
S. parasanguinis		*S. parasanguinis*
S. sanguinis	*S. sanguinis*	
***S. anginosus* Group**[a]		
S. anginosus	*S. anginosus*	
S. intermedius		*S. intermedius*
S. constellatus	*S. constellatus*	
Nutritionally Variant Streptococci		
Abiotrophia defectiva *Granulicatella adiacens* *Granulicatella elegans*	*Abiotrophia defectiva* *Granulicatella adiacens* *Granulicatella elegans*	
Granulicatella para-adiacens		*Granulicatella para-adiacens*

[a]Formerly *S. milleri* group.

TABLE 202.2 Some Biochemical Characteristics of Viridans Streptococci

SPECIES	VOGES-PROSKAUER	ARGININE	ESCULIN	MANNITOL	SORBITOL
S. mutans	+	–	+	+	+
S. salivarius	+	–	+	–	–
S. anginosus	+	+	+	–	–
S. sanguinis	–	+	+	–	V
S. gordonii	–	+	+	–	V
S. mitis	–	–	–	–	V
S. oralis	–	–	V	–	–

V, Variable.

typically have a depressed center. In general, viridans streptococci are not groupable by Lancefield antisera, but important exceptions include the Lancefield group F streptococci of the *S. anginosus* group.

Microbiologically, it is important to differentiate viridans streptococci from those in groups A, B, C, and G streptococci; group D enterococci; and nonenterococcal group D streptococci. *S. pneumoniae* is a lancet-shaped diplococcus and does not form long chains typical of the viridans streptococci. *S. pneumoniae* is α-hemolytic and demonstrates optochin inhibition.[1]

Group D enterococci are bile soluble, grow in 6.5% NaCl broth, and are penicillin resistant. In contrast, *S. bovis, (S. gallolyticus),* a nonenterococcal group D streptococcus, is penicillin susceptible.

Streptococcus anginosus Group

The *S. anginosus* group differs from other viridans streptococci in its ability to cause invasive pyogenic infections, that is, particularly abscesses (brain, dental, lung, heart, liver, abdomen).[5,6] Clinically, the *S. anginosus* group behaves more like *Staphylococcus aureus* than the other viridans streptococci, which are relatively avirulent. Viridans "small colony" streptococci (originally known as "minute hemolytic streptococci"), the *S. anginosus* group, may be rapidly differentiated from other viridans streptococci by three key tests: a positive Voges-Proskauer (VP) test, arginine hydrolysis, and inability to ferment sorbitol (Table 202.3). If present, a deacetyl metabolite is responsible for the "caramel odor" and is a distinctive feature of *S. anginosus* colonies on solid media. Some isolates of the *S. anginosus* group may react with Lancefield A, C, F, or G group antisera, but if the isolate is Lancefield group F positive, then the organism is one of the *S. anginosus* group.

Nutritionally Variant Streptococci: *Abiotrophia* sp. and *Granulicatella* spp.

The NVS have aspects in common with the viridans streptococci but have distinctive features. Like the viridans streptococci, they are commensals of the oropharynx and GI tract. *Abiotrophia* sp. and *Granulicatella* spp. differ from other viridans streptococci in their growth requirements. For NVS culture, media must contain thiol compounds (L-cysteine or vitamin B_6 or pyridoxamine). There is no growth on solid subculture media unless supplemented with pyridoxal (vitamin B_6). Alternatively, using a *S. aureus* streak to provide thiol compounds, subculture produces satellite colonies ("satelliting") surrounding the *S. aureus* streak. NVS colonies closest to the streak have uniform coccal morphology on Gram stain but show increasing pleomorphism the further from the *S. aureus* cross-streak. Aside from their vitamin B_6 growth requirement, they are PYR positive, whereas the viridans streptococci are PYR negative. In blood cultures NVS appear as oval to bulbous bacilliform cocci in short chains resembling *Streptobacillus moniliformis,* and some have long filaments. Microbiologic clues to NVS on blood culture are gram-variable pleomorphic streptococci that fail to grow on unsupplemented solid media subculture.

Currently, NVS have been placed in two distinct genera consisting of four species: one *Abiotrophia* sp., that is, *Abiotrophia defectiva,* and three *Granulicatella* spp., that is, *Granulicatella adiacens*, *Granulicatella elegans*, and *Granulicatella para-adiacens.* Species are differentiated by hydrolysis of hippurate, arginine, galactosidase, glucuronidase, and carbohydrate fermentation.[1]

EPIDEMIOLOGY

Viridans Streptococci and the *Streptococcus anginosus* Group

The viridans streptococci are part of the normal microbiota of the mouth and GI tract. The concentration of viridans streptococci in the GI tract is greatest in the oropharynx. Colonization of the oral cavity varies by species, for instance, *S. mitis* and *S. anginosus* (buccal mucosa); *S. oralis*, *S. mitis*, and *S. sanguinis* (early dental plaque); *Streptococcus gordonii* (supragingival plaque); and *S. anginosus* (subgingival plaque).[7,8] The adherence of the oral viridans streptococci is directly proportional to capsule production, which is related to fibronectin adherence to oral epithelial cells, that is, fibronectin selectively promotes adherence of oral streptococci, such as *S. mutans*.[9,10] In hospitalized patients with impaired fibronectin function, decreased adherence of oral streptococci predisposes to colonization by other organisms, such as nosocomial gram-negative bacilli. The frequency of viridans streptococci causing SBE is directly related to their relative capsule production. During bacteremia originating in the oral cavity, viridans streptococci with polysaccharide capsules are able to adhere to damaged heart valves and initiate the development of valvular vegetations. After bacteremia adherence precedes colonization, and colonization precedes infection on damaged cardiac valves.[9,11] Viridans streptococcal strains, most numerous in the oropharynx, with the most abundant capsule production are the most frequent species to cause SBE on damaged heart valves. Of interest, although the *S. anginosus* group is an oral commensal and associated with dental plaque as are the other oral viridans streptococci,

TABLE 202.3 Viridans Streptococci: Clinical Infectious Disease Spectrum

	COMMON COLONIZATION SITES	NONPATHOGENIC AT SITE	FREQUENT INFECTIOUS MANIFESTATIONS
Viridans streptococci[a]	Oropharynx (not a cause of pharyngitis) Skin (not a cause of cellulitis or abscess) GI tract (not a cause of cholecystitis, appendicitis, diverticulitis) Female GU tract	Lung[b,c] Bone[c] (not a cause of osteomyelitis) Sacral decubitus ulcers[c] Pelvis Skin Urinary tract (kidney, bladder, prostate)	Dental caries SBE[d] Late PVE Bacteremia (in neutropenic hosts)
S. anginosus (*S. milleri*) group	Oropharynx Upper respiratory tract	Bone Skin Urinary tract (kidney, bladder, prostate)	Brain abscesses Dental abscesses Lung abscesses Empyema Hepatic abscesses Myocardial abscesses Abdominal abscesses Pelvic abscesses
NVS (*Granulicatella* spp., *Abiotrophia* sp.)	Oropharynx Upper respiratory tract	Lung Skin GI tract GU tract	SBE Bacteremia (in neutropenic hosts)

[a]*S. mitis* group, *S. mutans* group, *S. salivarius* group, *S. sanguinis* group, and NVS.
[b]May be isolated from abscesses.
[c]As a commensal/colonizer cultured from tissues commonly.
[d]CNS involvement (aseptic meningitis) emboli, mycotic aneurysm.
CNS, Central nervous system; *GI,* gastrointestinal; *GU,* genitourinary; *NVS,* nutritionally variant streptococci; *PVE,* prosthetic valve endocarditis; *SBE,* subacute endocarditis.

the *S. anginosus* group is a rare cause of SBE.[12] In addition, in the setting of decreased neutrophil numbers, such as neutropenia, in severely leukopenic oncology patients, viridans streptococci may cause primary bacteremia.[13,14,15]

Nutritionally Variant Streptococci: *Abiotrophia* sp. and *Granulicatella* spp.

The NVS were first described as a species closely related to *S. mitior* (*S. mitis*) but were found to be genetically unrelated. *Abiotrophia* sp. and *Granulicatella* spp., like viridans streptococci, are colonizers of the oropharynx, GI tract. As with other streptococci and staphylococci, some NVS strains may demonstrate "tolerance," that is, minimal bactericidal concentration (MBC) ≥ 32 × minimal inhibitory concentration (MIC). If antibiotic "tolerance" is present, it has important therapeutic implications.[16]

VIRULENCE

Viridans Streptococci

Except for *S. mitis* and *S. pneumoniae*, viridans streptococci lack the virulence factors of β-hemolytic streptococci, are relatively avirulent, and are not pathogenic for laboratory animals. To cause infection, viridans streptococci require impaired host defenses, for instance, severe leukopenia in oncology patients. Viridans streptococci are the most frequent pathogens in native valve SBE and late prosthetic valve endocarditis (PVE) pathogens. Viridans streptococci are not primary pathogens in meningitis, bone, skin, or urine infections. However, viridans streptococci are commonly cultured alone or with other colonizers and are often present in dental, hepatic, or GI abscesses. Before ascribing an infection to viridans streptococci and considering the causative organism a pathogen, the organism should be repeatedly isolated (in pure culture) from sterile body sites.

In viridans streptococcal SBE virulence is determined by lipoteichoic acid (fibronectin adhesin). After adherence to damaged cardiac valves, viridans streptococci promote platelet aggregation via tissue factor, which is the initial step in the formation of cardiac vegetations.[11] Viridans streptococci are the most frequent pathogens causing native valve SBE in individuals with previous heart valve damage due to rheumatic heart disease, mitral valve prolapse, or degenerative valvular disease.[17,18] Viridans streptococci are important pathogens in late prosthetic valve endocarditis (not early PVE). With normal heart valves, repeated bacteremias from the oral cavity are common but do not result in SBE. The ability of viridans streptococci to cause SBE is directly related to the amount of polysaccharide (dextran) capsule produced and is species dependent. Strains with more abundant capsules are the most frequent SBE pathogens; conversely, strains with little or no capsule, such as *S. mitis,* are infrequent causes of SBE.

S. mutans is particularly associated with dental caries. Adherence to dental enamel is the initial step in caries development and is mediated by glucan. *S. mutans* glucan-mediated colonization occurs and in the presence of fermented sucrose produces acid that damages the enamel.

S. anginosus group, unlike other viridans streptococci, produces a variety of hydrolytic enzymes, such as hyaluronidase and DNase. Some species are able to use sialic acid as a sole carbon source and may be a growth factor for these organisms. Some species, for instance, *S. mitis,* produce superantigens that stimulate nonspecific T-lymphocyte proliferation.[19] Superantigens are potent inducers of cytokine release in systemic infections.

Streptococcus anginosus Group

Strains of *S. anginosus* group blunt chemotaxis and are relatively resistant to neutrophil killing.[20] The mechanism of abscess formation by the *S. anginosus* remains unknown. The *S. anginosus* group rarely causes SBE, but when it does, infection is often complicated by myocardial abscess with heart block. Species of the *S. anginosus* group may be cultured from abscesses alone or with other viridans streptococci.

Nutritionally Variant Streptococci: *Abiotrophia* sp. and *Granulicatella* spp.

Like viridans streptococci, NVS cause SBE on previously damaged heart valves. NVS causes SBE, which is often more severe than that caused by other viridans streptococci.[21] Among NVS organisms, *A. defectiva* seems especially suited to cause endovascular infection because of its ability to adhere to extracellular fibronectin.[22] Like other viridans streptococci, NVS may cause bacteremia in severely neutropenic oncology patients.

CLINICAL MANIFESTATIONS

Abscesses: *Streptococcus anginosus* Group

S. anginosus group organisms are frequent isolates in head and neck abscesses in pure culture or together with what used to be called the "oral pigmented *Bacteroides,*" for instance, *Prevotella melaninogenica*. Organisms of the *S. anginosus* group are often cultured from brain abscesses with or without other viridans streptococci. Brain abscesses do not result from viridans streptococcal SBE but result from bacteremia with central nervous system (CNS) seeding occurring in patients with suppurative lung disease, such as bronchiectasis, lung abscess, or cyanotic heart disease (R→L shunts). Alternatively, brain abscesses may result from spread from a contiguous focus.

Aseptic Meningitis: Viridans Streptococci

Not uncommonly, SBE due to viridans streptococci may be accompanied by seeding of the cerebrospinal fluid (CSF), clinically manifested as "aseptic meningitis." In this form there is an aseptic/viral CSF profile, with Gram stain/culture negativity with normal glucose and mild lymphocytic pleocytosis. This is in contrast to *S. aureus* acute bacterial endocarditis (ABE), in which the CSF seeding results in acute bacterial meningitis (ABM), showing a CSF "septic profile" with CSF Gram stain/culture positivity for *S. aureus*.

CNS emboli from viridans streptococcal SBE usually occurs in the terminal branches of the middle cerebral artery. The most common embolic CNS manifestation of viridans streptococci is an embolic stroke or mycotic aneurysm. Most mycotic aneurysms are asymptomatic, but rupture results in intracranial hemorrhage.

Subacute Bacterial Endocarditis: Viridans streptococci, *Streptococcus anginosus,* and Nutritionally Variant Streptococci

In the preantibiotic era, viridans streptococci accounted for approximately 75% of cases of IE. At the present time their relative frequency in endocarditis has declined to as low as 20%.[23] This change in epidemiology largely reflects an increase in the number of patients acquiring staphylococcal endocarditis in association with injection drug use, intravenous (IV) catheters, or prosthetic valves, and a decrease in the overall incidence of streptococcal endocarditis in industrialized nations.[24] In patients with SBE due to viridans streptococci, fevers usually are low grade (<102°F) and without rigors. Essentially all adults with native valve SBE have a cardiac murmur secondary to prior cardiac valvular damage. In viridans streptococcal SBE, splenomegaly and peripheral manifestations are a function of time. Of importance, peripheral adenopathy or hepatomegaly are not features of viridans streptococcal SBE and should suggest an alternative diagnosis. Viridans streptococci are also important pathogens in late-onset PVE. With the exception of the *S. anginosus* group, intracardiac abscesses or heart block are not clinical features of viridans streptococcal SBE. The diagnosis of SBE is based on the presence of fever, cardiac murmur, valvular vegetation, and continuous high-grade bacteremia due to an SBE pathogen, such as viridans streptococci. As the name suggests, SBE onset is subacute with low-grade fevers without chills. The fever in viridans streptococcal SBE has no particular pattern or periodicity, but it usually is prolonged and low grade. Night sweats and weight loss without anorexia may occur. Eye involvement is common, with conjunctival hemorrhage and/or Roth spots. The longer that SBE has been present, the more common are the peripheral manifestations.[25] Mild splenomegaly (nontender) is a common finding. Because hepatomegaly is not a feature of SBE, if present alone or with splenomegaly, an alternative explanation for liver enlargement should be sought. Alternatively, acute onset of otherwise unexplained hemorrhagic stroke, blindness, or abdominal pain due to a splenic infarct may suggest the diagnosis of SBE. A cardiac murmur with SBE is nearly always present, but there will not be a valvular murmur if related to a ventricular septal

defect. In contrast to new or changing murmurs, ABE murmurs are unchanging. Native valve viridans streptococcal SBE is diagnosed based on the presence of fever, cardiac murmur, continuous high-grade bacteremia, and a valvular vegetation by cardiac echocardiography.

In an adult with a cardiac murmur, even with low-grade fevers, a cardiac vegetation, and peripheral manifestation of SBE, the growth of viridans streptococci in one or two blood cultures is not diagnostic of SBE. With only one or two blood cultures positive for viridans streptococci, the clinician should consider the blood culture isolates a skin bacterial contaminant. Aside from the clinical findings described, the diagnosis of viridans streptococcal SBE requires the presence of high-grade continuous bacteremia. Streptococcal bacteremia, fever, murmur, cardiac vegetation, and peripheral manifestations without high-grade continuous viridans cultures should suggest the possibility of a SBE mimic, for instance, marantic endocarditis and Libman-Sacks endocarditis. The systemic embolic potential of viridans streptococcal SBE is directly related to vegetation size.

Typical nonspecific laboratory test abnormalities associated with viridans streptococcal SBE include an otherwise unexplained highly elevated erythrocyte sedimentation rate, mild leukocytosis, mild anemia (of chronic disease), and occasionally thrombocytosis. Unless there is associated heart failure, serum aminotransferases are not elevated. Microscopic hematuria is common and due to the focal glomerulonephritis that is the most common renal manifestation of SBE. *S. anginosus* group bacteria clinically behave like *S. aureus* with ABE and myocardial abscesses.

The NVS are a rare cause of SBE. NVS should be suspected as likely pathogens in SBE with positive blood cultures for streptococci that fail to grow on subculture. Cardiac vegetations are larger with NVS than viridans streptococcal SBE, but clinical manifestations of NVS SBE are often more subtle than viridans streptococcal SBE. Nevertheless, mortality of NVS SBE is higher than viridans streptococci SBE (Table 202.4).

Positive Blood Cultures and Nonsterile Body Sites: Viridans Streptococci

Viridans streptococci that are not invasive and relatively avirulent are commonly cultured from skin, sacral decubitus ulcers, and are common blood culture contaminants.[26] Unlike group D enterococci, viridans streptococci do not cause urinary tract infections. They are predominately colonizers of the oropharynx, GI tract, and skin. Until proven otherwise, culture of viridans streptococci from nonsterile sites alone or with other organisms should be considered as colonizers and not pathogens. Repeated isolation in pure culture from sterile body sites may indicate a pathogenic role, but microbiologic results should always be interpreted in the appropriate clinical context. Having blood cultures in which only one or two are positive for viridans streptococci argues against a diagnosis of SBE. High-grade (3/4–4) continuous viridans streptococcal bacteremia suggests SBE until proven otherwise (see Table 202.3).

Primary viridans streptococcal bacteremia may occur in patients with profound/prolonged neutropenia secondary to chemotherapy.[27,28] Viridans streptococci may gain bloodstream access from colonized intestinal mucosa damaged by chemotherapy. Fatality rates among neutropenic patients with bacteremia caused by penicillin-resistant viridans streptococci have been higher than for penicillin-susceptible strains.[29,30]

TABLE 202.4 Clinical Spectrum of Group C and G Streptococci

	GROUP C STREPTOCOCCI	GROUP G STREPTOCOCCI
Habitat	*Normal flora* Oropharynx Skin Female genital tract	*Normal flora* Oropharynx Skin Female genital tract
Predisposing factors	Animal or bird contact Ingestion of unpasteurized dairy products (milk, cheese) Malignancy Alcohol abuse DM	Malignancy Alcohol abuse DM Lymphedema Elderly IVDA
Colonization common	Oropharynx Skin	Oropharynx Skin
Rare causes of infections	1° bacteremia UTIs Osteomyelitis Septic arthritis CAP ABM (secondary to bacteremia)	1° bacteremia UTIs Osteomyelitis Septic arthritis ABM (2° to bacteremia)
Uncommon infections	ABM (2° to ABE) Brain abscess (2° to ABE) Endophthalmitis CAP Puerperal sepsis[a] Endometritis ABE[b,c]	ABM (2° to ABE) Brain abscess (2° to ABE) CAP Endophthalmitis Puerperal sepsis[a] Endometritis ABE[b,c]
Common infectious manifestations	Cellulitis (often recurrent) Pharyngitis[d] Septic arthritis[e,f]	Cellulitis (often recurrent) Pharyngitis Wound infections[a] Septic arthritis 2° bacteremia (from any of the above)
Postinfectious and immune manifestations	AGN Reactive arthritis	

[a]Nosocomial infections.
[b]Myocardial abscess, rapid valvular destruction, paravalvular abscess, congestive heart failure, and septic emboli.
[c]Skin usual source.
[d]May be severe.
[e]With normal and preexisting joint damage. Native joint septic arthritis usually polyarticular.
[f]2° bacteremia from cellulitis or endocarditis.
1°, Primary; *2°,* secondary; *ABE,* acute bacterial endocarditis; *ABM,* acute bacterial meningitis; *AGN,* acute glomerulonephritis; *CAP,* community-acquired pneumonia; *DM,* diabetes mellitus; *GCS,* group C streptococci; *GGS,* group G streptococci; *IVDA,* intravenous drug abuser; *UTI,* urinary tract infection.

THERAPY: VIRIDANS STREPTOCOCCI

Subacute Bacterial Endocarditis

Recommended regimens for treatment of streptococcal endocarditis are based largely on clinical observations and experimental animal models of endocarditis.[31] Optimal antibiotic selection for the therapy of viridans streptococcal endocarditis is based on two primary therapeutic considerations. First, the antibiotic selected should have a high degree of activity against the pathogen. Second, as important a consideration is achieving therapeutically effective concentrations at the site of infection, for instance, with infected cardiac valvular vegetation. Using pharmacokinetically based dosing, dosing interval, and duration, eradication of the bacteremic component of SBE is relatively straightforward. However, eradicating the source infection is critical to therapeutic success with SBE, that is, the ability of the selected antibiotic to sterilize the infected heart valve vegetation. With appropriate antibiotic therapy for viridans streptococcal SBE, elimination of the organism from the blood is rapid and easily achieved. Viridans streptococcal SBE is treated for weeks (see Chapter 80) so as to penetrate and sterilize the cardiac vegetation. With appropriate antimicrobial therapy, the continuous bacteremia of viridans streptococcal SBE rapidly resolves. Viridans streptococcal SBE relapses are rare with adequate duration of therapy. Cardiac vegetations decrease in size during effective antimicrobial therapy and usually completely resolve with therapy.

Meningitis: Viridans Streptococci

Despite the frequency with which viridans streptococci cause bacteremia, they are an uncommon cause of meningitis, accounting for only 0.3% to 5% of culture-proven cases.[32,33] Bacteremic meningitis in the absence of cardiac involvement has been described primarily in severely immunocompromised patients.[34] Viridans streptococcal SBE is often accompanied by systemic emboli. Clinically, CNS embolization may manifest as "aseptic meningitis." Typically, the CSF shows a mild lymphocytic pleocytosis, but viridans streptococci are not usually cultured from the CSF. Culture of viridans streptococci from CSF in a patient with viridans streptococcal SBE usually represents skin contamination

of the specimen. In such situations Gram staining of the CSF will be negative due to the few skin organisms contaminating the CSF culture medium. In a series of 43 patients from whom various species of α-hemolytic streptococci were isolated from CSF culture, only eight isolates (19%) were determined to be clinically relevant.[35]

Because the treatment of viridans streptococcal SBE is with high-dose penicillin or a β-lactam, additional CSF penetration is unnecessary. However, therapeutic CSF levels are an unintended effect that occurs as a result of high-dose endocarditis regimens, which are the same as for meningeal dosing, for instance, penicillin G 3 million units, IV, every 4 hours, or ceftriaxone 2 g, IV, every 24 hours. Although primary meningitis due to viridans streptococci remains rare, it can occur after medical procedures. In a review of bacterial meningitis occurring after dural puncture, streptococci were responsible for greater than 50% of the 179 cases.[36] Spinal and epidural anesthesia, myelography, and diagnostic lumbar puncture were the most common predisposing events. Iatrogenic viridans streptococcal meningitis has been reported in association with failure to adhere to infection control measures while performing lumbar puncture, especially regarding the use of face masks.[37] The same infection control measure may be important in preventing viridans streptococcal infection during joint injection.[38]

Endophthalmitis: Viridans Streptococci

With the increased use of intravitreal injections for macular degeneration and other conditions, viridans streptococci are an emerging pathogen in patients with endophthalmitis. A retrospective study of more than 33,000 injections at one large center showed that, although the overall rate of endophthalmitis was very low (13 cases over 10 years, for a rate of 0.04%), postinjection viridans streptococcal endophthalmitis occurred much more rapidly and had far worse final visual outcomes than cases caused by other organisms.[39] An outbreak of 12 patients with postinjection endophthalmitis, most caused by *S. mitis*/*S. oralis*, was linked to preparation of syringes of bevacizumab at a compounding pharmacy.[40]

Reactive and Septic Arthritis: Viridans Streptococci, Group C *Streptococcus*, and Group G *Streptococcus*

Reactive arthritis is the most common manifestation of viridans streptococcal SBE. As with CNS involvement, viridans streptococci are not culturable from synovial fluid in reactive arthritis. However, with some viridans streptococci, for instance, GCS or GGS, septic arthritis may occur from a nonendocarditis-related bacteremia. NVS septic arthritis remains rare, and specific ribosomal RNA polymerase chain reaction assays have been developed to aid in the identification of NVS.[41] With septic arthritis, antibiotic selection is based on the activity of the antibiotic against GCS or GGS and the ability of the antibiotic to penetrate synovial fluid in therapeutically effective concentrations. This is readily accomplished with β-lactam therapy, but synovial fluid penetration is suboptimal with vancomycin.

Abscesses: *Streptococcus anginosus* Group

Most viridans streptococci do not form abscesses, but abscess formation is particularly associated with the *S. anginosus* group. Abscesses may occur in many organs. Large abscesses, such as in the liver and abdomen, usually require drainage for source control. To be effective, abscess drainage must be adequate, and partially or completely drained abscesses usually require additional drainage and are unlikely to resolve with antibiotic therapy alone. Antibiotic penetration into abscesses is suboptimal with antibiotics, and antibiotic therapy alone should not be expected to effectively eliminate large abscesses.

Resistance: Viridans Streptococci and Nutritionally Variant Streptococci—*Abiotrophia* sp. and *Granulicatella* spp.

Viridans streptococci remain highly susceptible (MIC ≤ 0.12 μg/mL for penicillin) to penicillin and β-lactams.[42] Resistance, if present, is "relative resistance" (MIC = 0.25–2 μg/mL for penicillin). MICs are easily exceeded in blood and cardiac vegetations with the high-dose β-lactam therapies used for SBE. Even highly resistant strains (MIC ≥ 4 μg/mL for penicillin) are susceptible to high-dose penicillin or β-lactam therapy.[43] S. *mitis* and *S. oralis* are relatively more resistant than other viridans streptococci.[44] Among the viridans streptococci resistance is mediated by alterations in penicillin-binding proteins and not via β-lactamases. Trimethoprim-sulfamethoxazole (TMP-SMX) and ciprofloxacin have little activity against the viridans streptococci and should not be used, and resistance to tetracyclines and macrolides is common.[45,46,47] Decreasing susceptibility to other agents, including the third-generation cephalosporins and clindamycin, has been reported.[48] Effective alternatives to β-lactams include linezolid, levofloxacin, dalbavancin, and tigecycline.[49–51] High-level resistance to daptomycin monotherapy may occur rapidly. Resistance to daptomycin may be prevented or overcome with concomitant treatment with gentamicin.[52,53,54]

Some viridans streptococci demonstrate "tolerance," that is, MBC ≥ 32× the MIC. Clinically, tolerance should be suspected when the organism appears susceptible in vitro but the infection fails to clear even with appropriate antibiotic doses.[55] Gentamicin may be added to β-lactam therapy in the treatment of viridans streptococcal SBE to overcome such tolerance.[56] With SBE due to viridans streptococci, resistance is, in part, related to the abundance of capsular polysaccharide, and gentamicin added to a β-lactam decreases the relapse rate.[57] With uncomplicated viridans streptococcal SBE, duration of therapy can be as short as 2 weeks. If treated for 4 weeks, gentamicin may be given during the initial 2 weeks of therapy and may enhance outcomes.[57] Therapeutically achievable antibiotic concentrations in cardiac vegetations exceed the MIC of even "relatively resistant" strains of viridans streptococcal SBE. The prolonged duration of therapy of viridans streptococcal SBE is necessary for eradication of the organisms in the privileged site of infected vegetations.

Because NVS have unique growth requirements, uncommon recovery from clinical specimens, and difficulties in standardizing and interpreting testing methodologies, limited antimicrobial susceptibility data for these organisms are available. Approximately 33% to 67% of strains are relatively resistant (MIC, 0.25–2.0 μg/mL), and some isolates are highly resistant to penicillin (MIC ≥ 4 μg/mL).[58] Treatment of NVS, which are usually relatively resistant to penicillin, is usually 4 to 6 weeks with penicillin or β-lactam plus gentamicin for the initial 2 weeks.[56,57]

GROUPS C AND G STREPTOCOCCI

Group C Streptococci

Habitat

GCS are primarily animal pathogens, that is, of horses, cows, and swine. *S. equi* subsp. *zooepidemicus* causes significant, often epidemic, infections in domestic animals (horses, cattle, sheep, and pigs). It is not considered part of the normal human microbiota. Human infection is uncommon and is often reported in those with immune compromise; cases have been associated with consumption of homemade cheese and unpasteurized cow's milk and in humans who have had direct contact with animals.[59,60] However, colonization of GCS in the upper respiratory tract is relatively common.[61] In total, human infections are generally regarded as zoonotic and transmitted by ingestion of contaminated milk or dairy products.

Microbiology

Lancefield GCS have a polysaccharide capsule and may be α-, β-, or γ-hemolytic on sheep blood agar. GCS resemble GAS in some respects, but the terminal antigenic carbohydrate determinant is *N*-acetyl-galantamine in GCS, rather than *N*-acetylglucosamine as in GAS. GCS may resemble GAS on sheep blood agar. The appearance of large and small colony variants of groups C and G streptococci can make identification challenging. They are differentiated on the basis of biochemical tests, that is, VP negative and β-glucosidase positive, but some variants are VP positive and β-glucosidase negative. Because of variability in bacitracin testing with GCS, bacitracin testing cannot reliably differentiate GCS from GAS, and identification depends on group-specific antisera.[1] Unlike GAS, GCS are usually susceptible to TMP-SMX, whereas clindamycin resistance is uncommon among GCS but has been reported.[62]

Virulence
As with GAS, the primary virulence factors for GCS are the hyaluronic acid capsule and an M protein. GCS virulence is related to the abundance of its mucoid capsule, and some strains produce hemolysins.[1,63]

Clinical Manifestations
Human GCS infections may manifest clinically as pharyngitis, cellulitis, and only rarely as pneumonia, SBE, or meningitis.[60,64–67]

After colonization of the oropharynx, epidemics of GCS pharyngitis have occurred among college students.[68] Clinically, GCS pharyngitis resembles GAS pharyngitis, with fever, exudative pharyngitis, and anterior cervical adenopathy.[69–72] Of importance, like GAS pharyngitis, GCS pharyngitis may also elevate the antistreptolysin titer. However, acute rheumatic fever has not been linked to GCS pharyngitis.[73] GCS pharyngitis is usually less severe than GAS pharyngitis.[74]

In addition to the oropharynx, GCS are common colonizers of skin and female genitourinary (GU) tract. Like GAS, GCS may cause cellulitis or erysipelas. In parturient women GCS may cause puerperal sepsis or toxic shock syndrome. Nosocomial outbreaks have occurred in maternity units and burn wards.[75–77] Community-acquired pneumonia (CAP) rarely may be due to GCS and may be complicated by empyema.

Infections are most common in patients with cirrhosis, diabetes, and malignancy. Because skin colonization is common, positive blood cultures due to contamination should be differentiated from true bacteremia. Because continuous bacteremia is a feature of SBE, clinically the diagnosis of SBE should be made only with otherwise unexplained high-grade/sustained bacteremia. In patients with prolonged GCS bacteremia and clinical findings of SBE, a presumptive diagnosis may be made. GCS meningitis is usually due to CNS seeding secondary to endocarditis and may be complicated by brain abscess or subdural empyema.[66,78,79] Meningitis cases have been reported in association with ingestion of unpasteurized goat's milk[80] and from frequent contact with horses.[81]

Treatment
The antimicrobial agent of choice for group C β-hemolytic streptococci remains penicillin.[82] Other agents with good in vitro activity include amoxicillin, ureidopenicillins, cefazolin, cefotaxime, vancomycin, linezolid, and dalbavancin. Oxacillin and nafcillin are not effective. However, aside from vancomycin, the clinical experience with antimicrobial agents other than penicillin is limited. Resistance of GCS is about 30% to tetracycline, 25% to erythromycin, and 10% to ciprofloxacin. Two isolates had intermediate susceptibility to clindamycin.[83] Macrolide resistance is widespread in many countries.[63] Tolerance to penicillin has been reported in GCS, with MBCs ranging from 32- to 512-fold higher than the MICs.[84,85]

The addition of gentamicin or rifampin to a β-lactam or vancomycin results in bactericidal activity against GCS.[84,85] A marked synergy for killing of GCS by penicillin plus gentamicin has also been demonstrated, independent of penicillin tolerance. Although the clinical relevance of these findings is uncertain, combination therapy for patients with severe infections, such as endocarditis, meningitis, septic arthritis, or bacteremia in neutropenic hosts, caused by GCS should be considered.

GROUP G STREPTOCOCCI
GCS are rare causes of CAP. The clinical presentation is similar to GAS CAP, that is, segmental/lobar infiltrates with a moderate/large serosanguinous pleural effusion. [86]

Habitat
GGS are normal commensals of the oropharynx, skin, GI tract, and female GU tract.

Microbiology
GGS are characterized by two group-specific capsular polysaccharides—galactosamine and rhamnose—and GGS are usually β-hemolytic, resembling GAS. Animal, but not human, strains ferment trehalose. As with GCS, GGS produce large and small colonies, which can lead to misidentification. In some cases GGS are susceptible to bacitracin, as are GAS.

Virulence
As with GAS, M protein is the major virulence factor of GGS. M protein is protective against phagocytosis. GGS also produce C5a peptidase, which inactivates C5a chemotactic factor and fibronectin-binding protein.[1]

Clinical Manifestations
Infections due to GCS are often more severe than with other streptococci, particularly in patients with malignancy. GGS occurs in patients with cirrhosis, diabetes, and those on steroids or immunosuppressive therapy, and in IV drug abusers. GGS frequency colonizes the oropharynx but may cause acute pharyngitis, often in outbreaks.[87,88] Clinically, GGS pharyngitis resembles GAS pharyngitis but is often more severe. In contrast to GAS pharyngitis, which occurs in those younger than 30 years, GGS pharyngitis is most frequent in the elderly. As with GAS, GCS or GGS may be cultured from the throat in those with an underlying viral pharyngitis, such as due to Epstein-Barr virus. As with GCS, infection with GGS is not a cause of acute rheumatic fever.[73] Culture from the throat indicates presence (colonization) and is not diagnostic of a pathogenic role (see Table 202.4).

GGS are common skin colonizers, and skin infections also are common.[89] Most frequently, GGS occur in cellulitis and may be accompanied by bacteremia. Septic arthritis after bacteremia may result in patients with underlying joint disease and those with prosthetic joints.[90] Septic arthritis due to GCS is often polyarticular, and osteomyelitis may occur with septic arthritis. Osteomyelitis due to GGS occurs primarily in the elderly with malignancies and those with cirrhosis, osteoarthritis, or prosthetic joint materials, or with impaired host defenses.[91] GGS rarely causes CAP or SBE.[86,92] GGS SBE is often complicated by embolic complications, congestive heart failure, and acute bacterial meningitis.[78,93–95] Uncommonly, GGS infections may be the causes of puerperal sepsis.[67] Secondary bacteremia may follow skin or joint infections, but primary bacteremia also may occur, but rarely.[96,97] Although GCS are associated with malignancy, the association is even stronger with GGS.[65,67,98] Of importance, otherwise unexplained GGS bacteremia should prompt a search for an underlying malignancy or other structural lesions in the GI tract.

Treatment
GGS are also susceptible in vitro to multiple antimicrobial agents, including penicillin G, ureidopenicillins, most cephalosporins, vancomycin, linezolid, and dalbavancin.[50,83,99] The most active drugs are penicillin, ampicillin, and cefotaxime; however, oxacillin and nafcillin are not effective therapeutic agents. Clindamycin, erythromycin, and tetracycline have relatively poor activity against GGS. Resistance to tetracyclines, clindamycin, and macrolides is increasing.[100] Penicillin tolerance is not a major feature of GGS, and it has been demonstrated only in the presence of a high inoculum.

Streptococcus suis
S. suis is a major pathogen in swine populations worldwide, and human infection can result in persons who have had close contact with sick animals or contaminated pork products.[59] Most human cases have arisen in Southeast Asia due to farm contacts between humans and pigs. Although most infections have been sporadic, there was a large outbreak in Southwest China in 2005.[101]

Sepsis and meningitis are major manifestations of *S. suis* infection, and hearing loss is a frequent complication. In contrast to the auditory nerve damage, which can occur as a complication of *S. pneumoniae* and *Haemophilus influenzae* meningitis, the cause of deafness in patients with *S. suis* infection is labyrinthitis. This is an important distinction because *S. suis* meningitis may be associated with more profound hearing loss compared with other causes of acute bacterial meningitis.[102] Despite *S. suis* generally being very susceptible in vitro to penicillin, relapses have been seen in patients with meningitis that has been appropriately treated. Relapse should prompt an assessment for occult foci of infection

and decreased antimicrobial susceptibility, but, in the absence of those two factors, longer courses of therapy may be required.[103]

Viridans-Like Organisms

Rothia

Rothia mucilaginosa (formerly *Stomatococcus mucilaginosus*) is a gram-positive aerobic coccus that was traditionally found as a cause of oral, cutaneous, and CNS infections in impaired hosts. Infections in immunocompetent hosts, including meningitis, necrotizing fasciitis, and prosthetic joint infection, have also been reported.[104–106] Patients with hematologic malignancies and profound neutropenia with central-line catheters have been found to be at higher risk of developing *Rothia* infection.[107] Most *Rothia* strains are susceptible to ceftriaxone, vancomycin, carbapenems, and levofloxacin.[108]

Pediococcus

Pediococcus spp. are gram-positive aerobic cocci that have caused nosocomial infections, particularly bacteremia and intraabdominal infections. They are intrinsically resistant to vancomycin; therapy has traditionally been with β-lactams, but the successful use of daptomycin has also been reported.[109]

Key References

The complete reference list is available online at Expert Consult.

1. Ruoff KL, Whiley RA, Beighton D. *Streptococcus*. In: Murray PR, Baron EJ, Jorgensen JH, et al, eds. *Manual of Clinical Microbiology*. 8th ed. Washington, DC: American Society for Microbiology; 2003:405–421.
2. Vogkou CT, Vlachogiannis NI, Palaiodims L, et al. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. *Eur J Clin Microbiol Infect Dis*. 2016;35:1227–1245.
4. Bruckner DA, Colonna P, Bearson BL. Nomenclature for aerobic and facultative bacteria. *Clin Infect Dis*. 1999;29:713–723.
8. Mitchell J. *Streptococcus mitis:* walking the line between commensalism and pathogenesis. *Mol Oral Microbiol*. 2011;26:89–98.
10. Krzysciak W, Jurczak A, Koscielniak D, et al. The virulence of *Streptococcus mutans* and the ability to form biofilms. *Eur J Clin Microbiol Infect Dis*. 2014;33:499–515.
11. Scheld WM, Valone JA, Sande MA. Bacterial adherence in the pathogenesis of endocarditis. Interaction of bacterial dextran, platelets, and fibrin. *J Clin Invest*. 1978;61:1394–1404.
14. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis*. 2002;34:1524–1529.
16. Tellez A, Ambrosioni J, Llopis J, et al. Epidemiology, clinical features, and outcomes of infective endocarditis due to *Abiotrophia* species and *Granulicatella* species: report of 76 cases, 200-2015. *CID*. 2018;66:104–111.
17. Van der Meer JTM, Thompson J, Valkenburg HA, et al. Epidemiology of bacterial endocarditis in the Netherlands: patient characteristics. *Arch Intern Med*. 1992;152:1863–1868.
24. Hoen B, Duval X. Infective endocarditis. *N Engl J Med*. 2013;368:1425–1433.
25. Bush LM, Johnson CC. Clinical syndrome and diagnosis of endocarditis. In: Kaye D, ed. *Infective Endocarditis*. 2nd ed. Philadelphia: Raven Press; 1992:99–115.
27. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis*. 1992;14:1201–1207.
29. Koren P, Krcmery V Jr. Viridans streptococcal bacteremia due to penicillin-resistant and penicillin-sensitive streptococci: analysis of risk factors and outcome in 60 patients from a single cancer centre before and after penicillin is used for prophylaxis. *Scand J Infect Dis*. 1997;29:245–249.
30. Mrazova M, Docze A, Buckova E, et al. Prospective national survey of viridans streptococcal bactaeremia risk factors, antibacterial susceptibility and outcome of 120 episodes. *Scand J Infect Dis*. 2005;37:637–641.
31. Tunkel AR, Scheld WM. Experimental models of endocarditis. In: Kaye D, ed. *Infective Endocarditis*. 2nd ed. New York: Raven Press; 1992:37–56.
33. Enting RH, deGans J, Blankevoort JP, et al. Meningitis due to viridans streptococci in adults. *J Neurol*. 1997;244:435–438.
34. Villablanca JG, Steiner M, Kersey J, et al. The clinical spectrum of infections with viridans streptococci in bone marrow transplant patients. *Bone Marrow Transplant*. 1990;6:387–393.
38. Reeves KD, Horvat RT. Aerosolized alpha-hemolytic *Streptococcus* as a cause of knee sepsis after intra-articular injection: predisposing factors. *Am J Phys Med Rehab*. 2010;89:77–82.
39. Chen E, Lin MY, Cox J, et al. Endophthalmitis after intravitreal injection: the importance of viridans streptococci. *Retina*. 2011;31:1525–1533.
43. Hsu RB, Lin FY. Effect of penicillin resistance on presentation and outcome of nonenterococcal streptococcal endocarditis. *Cardiology*. 2006;105:234–239.
45. Suvuk S, Kaskatepe B, Cetin MA. Antimicrobial susceptibility against penicillin, ampicillin, and vancomycin of viridans group streptococci in oral microbiota of patients at risk of infective endocarditis. *Infez Med*. 2016;24:190–193.
48. Liao CH, Teng LJ, Hsueh PR, et al. Nutritionally variant streptococcal infections at a University Hospital in Taiwan: disease emergence and high prevalence of beta-lactam and macrolide resistance. *Clin Infect Dis*. 2004;38:452–455.
49. Moet GJ, Dowzicky MJ, Jones RN. Tigecycline (GAR-936) activity against *Streptococcus gallolyticus (bovis)* and viridans group streptococci. *Diagn Microbiol Infect Dis*. 2007;57:333–336.
50. Jones RN, Stilwell MG. Comprehensive update of dalbavancin activity when tested against uncommonly isolated streptococci, *Corynebacterium* spp., *Listeria monocytogenes*, and *Micrococcus* spp. (1357 strains). *Diagn Microbiol Infect Dis*. 2013;76:239–240.
51. Băncescu G, Neagu AS, Radu-Popescu M, et al. Susceptibility testing of *Streptococcus pneumoniae* and viridans streptococcal isolates against: quinolones, oxazolidinones and glycopeptides. *Rev Med Chir Soc Med Nat Iasi*. 2012;116:286–290.
52. Akins RL, Barber KE, Palmer KL. Pronounced heterogeneity observed in high-level daptomycin-resistant viridans group streptococci. *J Glob Antimicrob Resist*. 2016;7:159–166.
56. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.
57. Brusch JL. Medical management. In: Brusch JL, ed. *Infective Endocarditis. Management in the Era of Intravascular Devices*. New York: Informa Healthcare; 2007:273–284.
58. Zheng X, Freeman AF, Villafranca J, et al. Antimicrobial susceptibilities of invasive pediatric *Abiotrophia* and *Granulicatella* isolates. *J Clin Microbiol.* 2004;42:4323-4326.
62. Rolston KV, LeFrock JL, Schell RF. Activity of nine antimicrobial agents against Lancefield group C and group G streptococci. *Antimicrob Agents Chemother*. 1982;22:930–932.
63. Brandt CM, Spellerberg B. Human infections due to *Streptococcus dysgalactiae* subspecies *equisimilis*. *Clin Infect Dis*. 2009;49:766–772.
64. Armstrong D, Blevins A, Louria DB, et al. Groups B, C, and G streptococcal infections in a cancer hospital. *Ann NY Acad Sci*. 1970;174:511–522.
65. Auckenthaler R, Hermans PE, Washington JAII. Group G streptococcal bacteremia: clinical study and review of the literature. *Rev Infect Dis*. 1983;5:196–204.
67. Vartian C, Lerner PI, Shlaes DM, et al. Infections due to Lancefield group G streptococci. *Medicine (Baltimore)*. 1985;64:75–88.
70. Zaoutis T, Attia M, Gross R, et al. The role of group C and group G streptococci in acute pharyngitis in children. *Clin Microbiol Infect*. 2004;10:37–40.
72. Shah M, Centor RM, Jennings M. Severe acute pharyngitis caused by group C streptococcus. *J Gen Intern Med*. 2007;22:272–274.
74. Bramhachari PV, Kaul SY, McMillan DJ, et al. Disease burden due to *Streptococcus dysgalactiae* subsp. *equisimilis* (group G and C *Streptococcus*) is higher than that due to *Streptococcus pyogenes* among Mumbai school children. *J Med Microbiol*. 2010;59:220–223.
75. Teare EL, Smithson RD, Efstratiou A, et al. An outbreak of puerperal fever caused by group C streptococci. *J Hosp Infect*. 1989;13:337–347.
76. Korman TM, Boers A, Gooding TM. Fatal case of toxic shock-like syndrome due to group C *Streptococcus* associated with superantigen exotoxin. *J Clin Microbiol*. 2004;42:2866–2869.
77. Goldman DA, Breton SJ. Group C streptococcal surgical wound infections transmitted by an anorectal and nasal carrier. *Pediatrics*. 1978;61:235–237.
79. Rajasekhar A, Clancy CJ. Meningitis due to group C *Streptococcus:* a case report and review of the literature. *Scand J Infect Dis*. 2010;42:571–578.
82. Rolston KVI, LeFrock JL, Schell RF. Activity of nine antimicrobial agents against Lancefield group C and group G streptococci. *Antimicrob Agents Chemother*. 1982;22:930–932.
85. Rolston KVI, Chandraseker PH, LeFrock JL. Antimicrobial tolerance in group C and group G streptococci. *J Antimicrob Chemother*. 1984;13:389–392.
87. McCue JD. Group G streptococcal pharyngitis: analysis of an outbreak at a college. *JAMA*. 1982;248:1333–1336.
90. Bronze MS, Whitby S, Schaberg DR. Group G streptococcal arthritis: a case report and review of the literature. *Am J Med Sci*. 1997;313:239–243.
95. Bouza E, Meyer RD, Busch DF. Group G streptococcal endocarditis. *Am J Clin Pathol*. 1978;70:108–111.
99. Rolston KVI, Chandraseker PH, LeFrock JL. Antimicrobial tolerance in group C and group G streptococci. *J Antimicrob Chemother*. 1984;13:389–392.
102. Mai NT, Hoa NT, Nga TV, et al. *Streptococcus suis* meningitis in adults in Vietnam. *Clin Infect Dis*. 2008;46:659–667.
104. Rizvi M, Fatima N, Shukla I, et al. *Stomatococcus mucilaginosus* meningitis in a healthy 2-month-old child. *J Med Microbiol*. 2008;57:382–383.
108. Ramanan P, Barreto JN, Osmon DR, et al. *Rothia* bacteremia: a 10-year experience at Mayo Clinic, Rochester, Minnesota. *J Clin Microbiol*. 2014;52:3184–3189.
109. Suh B. Resolution of persistent *Pediococcus* bacteremia with daptomycin treatment: case report and review of the literature. *Diagn Microbiol Infect Dis*. 2010;66:111–115.

References

1. Ruoff KL, Whiley RA, Beighton D. *Streptococcus*. In: Murray PR, Baron EJ, Jorgensen JH, et al, eds. *Manual of Clinical Microbiology*. 8th ed. Washington, DC: American Society for Microbiology; 2003:405–421.
2. Vogkou CT, Vlachogiannis NI, Palaiodims L, et al. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. *Eur J Clin Microbiol Infect Dis*. 2016;35:1227–1245.
3. Guiliano S, Caccese R, Carfagna P, et al. Endocarditis caused by nutritionally variant streptococci: a case report and literature review. *Infez Med*. 2012;20:67–74.
4. Bruckner DA, Colonna P, Bearson BL. Nomenclature for aerobic and facultative bacteria. *Clin Infect Dis*. 1999;29:713–723.
5. Fazil T, Riddell S, Kiska D, et al. *Streptococcus anginosus* group bacterial infections. *Am J Med Sci*. 2017;354:257–261.
6. Guiliano S, Rubini G, Conte A, et al. *Streptococcus anginosus* group disseminated infection: case report and review of literature. *Infez Med*. 2012;20:145–154.
7. Frandsen EVG, Pedrazzoli V, Kilian M. Ecology of viridans streptococci in the oral cavity and pharynx. *Oral Microbiol Immunol*. 1991;6:129–133.
8. Mitchell J. *Streptococcus mitis:* walking the line between commensalism and pathogenesis. *Mol Oral Microbiol*. 2011;26:89–98.
9. Scheld WM, Strunk RW, Balian G, et al. Microbial adhesion to fibronectin in vitro correlates with production of endocarditis in rabbits. *Proc Soc Exp Biol Med*. 1985;180:474–482.
10. Krzysciak W, Jurczak A, Koscielniak D, et al. The virulence of *Streptococcus mutans* and the ability to form biofilms. *Eur J Clin Microbiol Infect Dis*. 2014;33:499–515.
11. Scheld WM, Valone JA, Sande MA. Bacterial adherence in the pathogenesis of endocarditis. Interaction of bacterial dextran, platelets, and fibrin. *J Clin Invest*. 1978;61:1394–1404.
12. Asam D, Spellerberg B. Molecular pathogenicity of *Streptococcus anginosus*. *Mol Oral Microbiol*. 2014;29:145–155.
13. Radocha J, Paterova P, Zavrelova A, et al. Viridans group streptococci bloodstream infections in neutropenic adult patients with hematologic malignancy: single center experience. *Folia Microbiol*. 2018;63:141–146.
14. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis*. 2002;34:1524–1529.
15. Engel A, Kern P, Kern WV. Levels of cytokines and cytokine inhibitors in the neutropenic patients with α-hemolytic *Streptococcus* shock syndrome. *J Infect Dis*. 1996;23:785–789.
16. Tellez A, Ambrosioni J, Llopis J, et al. Epidemiology, clinical features, and outcomes of infective endocarditis due to *Abiotrophia* species and *Granulicatella* species: report of 76 cases, 200-2015. *CID*. 2018;66:104–111.
17. Van der Meer JTM, Thompson J, Valkenburg HA, et al. Epidemiology of bacterial endocarditis in the Netherlands: patient characteristics. *Arch Intern Med*. 1992;152:1863–1868.
18. McKinsey DS, Ratts TE, Bisno AL. Underlying cardiac lesions in adults with infective endocarditis: the changing spectrum. *Am J Med*. 1987;82:681–688.
19. Matsushita K, Sugiyama A, Uchiyama T, et al. Induction of lymphocytes cytotoxic to oral epithelial cells by *Streptococcus mitis* superantigen. *J Dent Res*. 1996;75:927–934.
20. Wanahita A, Goldsmith EA, Musher D, et al. Interactions between human polymorphonuclear leukocytes and *Streptococcus milleri* group bacteria. *J Infect Dis*. 2002;185:85–90.
21. Adam EL, Siciliano RF, Gualandro DM, et al. Case series of infective endocarditis caused by *Granulicatella* species. *Int J Infect Dis*. 2015;31C:56–58.
22. Senn L, Entenza JM, Prod'hom G. Adherence of *Abiotrophia defectiva* and *Granulicatella* species to fibronectin: is there a link with endovascular infection? *FEMS Immunol Med Microbiol*. 2006;48:215–217.
23. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA*. 2002;288:75–81.
24. Hoen B, Duval X. Infective endocarditis. *N Engl J Med*. 2013;368:1425–1433.
25. Bush LM, Johnson CC. Clinical syndrome and diagnosis of endocarditis. In: Kaye D, ed. *Infective Endocarditis*. 2nd ed. Philadelphia: Raven Press; 1992:99–115.
26. Swenson FJ, Rubin SJ. Clinical significance of viridans streptococci isolated from blood cultures. *J Clin Microbiol*. 1982;15:725–727.
27. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis*. 1992;14:1201–1207.
28. Bilgrami S, Feingold JM, Dorsky D, et al. *Streptococcus viridans* bacteremia following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 1998;21:591–595.
29. Koren P, Krcmery V Jr. Viridans streptococcal bacteremia due to penicillin-resistant and penicillin-sensitive streptococci: analysis of risk factors and outcome in 60 patients from a single cancer centre before and after penicillin is used for prophylaxis. *Scand J Infect Dis*. 1997;29:245–249.
30. Mrazova M, Docze A, Buckova E, et al. Prospective national survey of viridans streptococcal bactaeremia risk factors, antibacterial susceptibility and outcome of 120 episodes. *Scand J Infect Dis*. 2005;37:637–641.
31. Tunkel AR, Scheld WM. Experimental models of endocarditis. In: Kaye D, ed. *Infective Endocarditis*. 2nd ed. New York: Raven Press; 1992:37–56.
32. Hoyne AL, Herzon H. *Streptococcus viridans* meningitis: a review of the literature and report of nine recoveries. *Ann Intern Med*. 1950;33:879–902.
33. Enting RH, deGans J, Blankevoort JP, et al. Meningitis due to viridans streptococci in adults. *J Neurol*. 1997;244:435–438.
34. Villablanca JG, Steiner M, Kersey J, et al. The clinical spectrum of infections with viridans streptococci in bone marrow transplant patients. *Bone Marrow Transplant*. 1990;6:387–393.
35. Nachamkin I, Dalton HP. The clinical significance of streptococcal species isolated from cerebrospinal fluid. *Am J Clin Pathol*. 1983;79:195–199.
36. Baer ET. Post-dural puncture bacterial meningitis. *Anesthesiology*. 2006;105:381–393.
37. Schneeberger PM, Janssen M, Voss A. α-Hemolytic streptococci: a major pathogen of iatrogenic meningitis following lumbar puncture. *Infection*. 1996;24:29–33.
38. Reeves KD, Horvat RT. Aerosolized alpha-hemolytic *Streptococcus* as a cause of knee sepsis after intra-articular injection: predisposing factors. *Am J Phys Med Rehab*. 2010;89:77–82.
39. Chen E, Lin MY, Cox J, et al. Endophthalmitis after intravitreal injection: the importance of viridans streptococci. *Retina*. 2011;31:1525–1533.
40. Goldberg RA, Flynn HW Jr, Isom RF, et al. An outbreak of streptococcal endophthalmitis after intravitreal injection of bevacizumab. *Am J Ophthalmol*. 2012;153:204–208.
41. Roggenkamp A, Leitritz L, Baus K, et al. PCR for detection and identification of *Abiotrophia* spp. *J Clin Microbiol*. 1998;36:2844–2846.
42. Prabhu RM, Piper KE, Baddour LM, et al. Antimicrobial susceptibility patterns among viridans group streptococcal isolates from infective endocarditis patients from 1971 to 1986 and 1994 to 2002. *Antimicrob Agents Chemother*. 2004;48:4463–4465.
43. Hsu RB, Lin FY. Effect of penicillin resistance on presentation and outcome of nonenterococcal streptococcal endocarditis. *Cardiology*. 2006;105:234–239.
44. Tuohy M, Washington JA. Antimicrobial susceptibility of viridans group streptococci. *Diagn Microbiol Infect Dis*. 1997;29:277–280.
45. Suvuk S, Kaskatepe B, Cetin MA. Antimicrobial susceptibility against penicillin, ampicillin, and vancomycin of viridans group streptococci in oral microbiota of patients at risk of infective endocarditis. *Infez Med*. 2016;24:190–193.
46. Chun S, Huh HJ, Lee NY. Species-specific difference in antimicrobial susceptibility among viridans group streptococci. *Ann Lab Med*. 2015;35:205–211.
47. Obszanska K, Kern-Zdanowicz I, Kozinska A, et al. *Streptococcus anginosus (milleri)* group strains isolated in Poland (1996-2012) and their antibiotic resistance patterns. *Pol J Microbiol*. 2016;65:33–41.
48. Liao CH, Teng LJ, Hsueh PR, et al. Nutritionally variant streptococcal infections at a University Hospital in Taiwan: disease emergence and high prevalence of beta-lactam and macrolide resistance. *Clin Infect Dis*. 2004;38:452–455.
49. Moet GJ, Dowzicky MJ, Jones RN. Tigecycline (GAR-936) activity against *Streptococcus gallolyticus (bovis)* and viridans group streptococci. *Diagn Microbiol Infect Dis*. 2007;57:333–336.
50. Jones RN, Stilwell MG. Comprehensive update of dalbavancin activity when tested against uncommonly isolated streptococci, *Corynebacterium* spp., *Listeria monocytogenes*, and *Micrococcus* spp. (1357 strains). *Diagn Microbiol Infect Dis*. 2013;76:239–240.
51. Băncescu G, Neagu AS, Radu-Popescu M, et al. Susceptibility testing of *Streptococcus pneumoniae* and viridans streptococcal isolates against: quinolones, oxazolidinones and glycopeptides. *Rev Med Chir Soc Med Nat Iasi*. 2012;116:286–290.
52. Akins RL, Barber KE, Palmer KL. Pronounced heterogeneity observed in high-level daptomycin-resistant viridans group streptococci. *J Glob Antimicrob Resist*. 2016;7:159–166.
53. García-de-la-Mària C, Pericas JM, Del Río A, et al. Early in vitro and in vivo development of high-level daptomycin resistance is common in mitis group streptococci after exposure to daptomycin. *Antimicrob Agents Chemother*. 2013;57:2319–2325.
54. Akins RL, Katz BD, Monahan C, et al. Characterization of high-level daptomycin resistance in viridans group streptococci developed upon in vitro exposure to daptomycin. *Antimicrob Agents Chemther*. 2015;59:2102–2112.
55. Handwerger S, Tomasz A. Antibiotic tolerance among clinical isolates of bacteria. *Rev Infect Dis*. 1985;7:368–386.
56. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.
57. Brusch JL. Medical management. In: Brusch JL, ed. *Infective Endocarditis. Management in the Era of Intravascular Devices*. New York: Informa Healthcare; 2007:273–284.
58. Zheng X, Freeman AF, Villafranca J, et al. Antimicrobial susceptibilities of invasive pediatric *Abiotrophia* and *Granulicatella* isolates. *J Clin Microbiol*. 2004;42:4323–4326.
59. Fulde M, Valentin-Weigand P. Epidemiology and pathogenicity of zoonotic streptococci. *Curr Top Microbiol Immunol*. 2013;368:49–81.
60. Bradley SF, Gordon JJ, Baumgartner DD, et al. Group C streptococcal bacteremia: analysis of 88 cases. *Rev Infect Dis*. 1991;13:270–280.
61. Nobbs AH, Lamont RJ, Jenkinson HF. *Streptococcus* adherence and colonization. *Microbiol Mol Biol Rev*. 2009;73:407–450.
62. Rolston KV, LeFrock JL, Schell RF. Activity of nine antimicrobial agents against Lancefield group C and group G streptococci. *Antimicrob Agents Chemother*. 1982;22:930–932.
63. Brandt CM, Spellerberg B. Human infections due to *Streptococcus dysgalactiae* subspecies *equisimilis*. *Clin Infect Dis*. 2009;49:766–772.
64. Armstrong D, Blevins A, Louria DB, et al. Groups B, C, and G streptococcal infections in a cancer hospital. *Ann NY Acad Sci*. 1970;174:511–522.
65. Auckenthaler R, Hermans PE, Washington JAII. Group G streptococcal bacteremia: clinical study and review of the literature. *Rev Infect Dis*. 1983;5:196–204.
66. Salata RA, Lerner PI, Shlaes DM, et al. Infections due to Lancefield group C streptococci. *Medicine (Baltimore)*. 1989;68:225–239.
67. Vartian C, Lerner PI, Shlaes DM, et al. Infections due to Lancefield group G streptococci. *Medicine (Baltimore)*. 1985;64:75–88.
68. Turner JC, Hayden GF, Kiselica D, et al. Association of group C β-hemolytic streptococci with endemic pharyngitis among college students. *JAMA*. 1990;264:2644–2647.
69. Cimolai N, Elford RW, Bryan L, et al. Do the β-hemolytic non-group A streptococci cause pharyngitis? *Rev Infect Dis*. 1988;10:587–601.
70. Zaoutis T, Attia M, Gross R, et al. The role of group C and group G streptococci in acute pharyngitis in children. *Clin Microbiol Infect*. 2004;10:37–40.
71. Meier FA, Centor RM, Graham L, et al. Clinical and microbiological evidence for endemic pharyngitis among adults due to group C streptococci. *Arch Intern Med*. 1990;150:825–829.
72. Shah M, Centor RM, Jennings M. Severe acute pharyngitis caused by group C streptococcus. *J Gen Intern Med*. 2007;22:272–274.
73. Bisno AL, Collins CM, Turner JC. M Proteins of Group C streptococci isolated from patients with acute pharyngitis. *J Clin Microbiol*. 1996;34:2511–2515.
74. Bramhachari PV, Kaul SY, McMillan DJ, et al. Disease burden due to *Streptococcus dysgalactiae* subsp. *equisimilis* (group G and C *Streptococcus*) is higher than that due to *Streptococcus pyogenes* among Mumbai school children. *J Med Microbiol*. 2010;59:220–223.
75. Teare EL, Smithson RD, Efstratiou A, et al. An outbreak of puerperal fever caused by group C streptococci. *J Hosp Infect*. 1989;13:337–347.
76. Korman TM, Boers A, Gooding TM. Fatal case of toxic shock-like syndrome due to group C *Streptococcus* associated with superantigen exotoxin. *J Clin Microbiol*. 2004;42:2866–2869.
77. Goldman DA, Breton SJ. Group C streptococcal surgical wound infections transmitted by an anorectal and nasal carrier. *Pediatrics*. 1978;61:235–237.

78. Daly MP. Group G streptococcal infection in an elderly patient. *South Med J*. 1992;85:43–44.
79. Rajasekhar A, Clancy CJ. Meningitis due to group C *Streptococcus*: a case report and review of the literature. *Scand J Infect Dis*. 2010;42:571–578.
80. Edwards AT, Roulson M, Ironside MJ. A milk-borne outbreak of serious infection due to *Streptococcus zooepidemicus* (Lancefield group C). *Epidemiol Infect*. 1988;101:43–51.
81. Ural O, Tuncer I, Dikici N, et al. *Streptococcus zooepidemicus* meningitis and bacteraemia. *Scand J Infect Dis*. 2003;35:206–207.
82. Rolston KVI, LeFrock JL, Schell RF. Activity of nine antimicrobial agents against Lancefield group C and group G streptococci. *Antimicrob Agents Chemother*. 1982;22:930–932.
83. Lloyd CA, Jacob SE, Menon T. Antibiotic resistant beta-hemolytic streptococci. *Indian J Pediatr*. 2007;74:1077–1080.
84. Portnoy D, Prentis J, Richards GK. Penicillin tolerance of human isolates of group C streptococci. *Antimicrob Agents Chemother*. 1981;20:235–238.
85. Rolston KVI, Chandraseker PH, LeFrock JL. Antimicrobial tolerance in group C and group G streptococci. *J Antimicrob Chemother*. 1984;13:389–392.
86. Dolinski SY, Jones PG, Zabransky RJ, et al. Group C streptococcal pleurisy and pneumonia: a fulminant case and review of the literature. *Infection*. 1990;18:239–241.
87. McCue JD. Group G streptococcal pharyngitis: analysis of an outbreak at a college. *JAMA*. 1982;248:1333–1336.
88. Gerber MA, Randolph MF, Martin NJ, et al. Community-wide outbreak of group G streptococcal pharyngitis. *Pediatrics*. 1991;87:598–603.
89. Siljander T, Karppelin M, Vahakuopus S, et al. Acute bacterial, nonnecrotizing cellulitis in Finland: microbiological findings. *Clin Infect Dis*. 2008;46:855–861.
90. Bronze MS, Whitby S, Schaberg DR. Group G streptococcal arthritis: a case report and review of the literature. *Am J Med Sci*. 1997;313:239–243.
91. Burkert T, Watanakunakorn C, Group G. *Streptococcus* septic arthritis and osteomyelitis: report and literature review. *J Rheumatol*. 1991;18:904–907.
92. Blair DC, Martin DB. β-Hemolytic streptococcal endocarditis: predominance of non-group A organisms. *Am J Med Sci*. 1978;276:269–277.
93. Venezio FR, Gullberg RM, Westenfelder GO, et al. Group G streptococcal endocarditis and bacteremia. *Am J Med*. 1986;81:29–34.
94. Smyth EG, Pallett AP, Davidson RN. Group G streptococcal endocarditis: two case reports, a review of the literature and recommendations for treatment. *J Infect*. 1988;16:169–176.
95. Bouza E, Meyer RD, Busch DF. Group G streptococcal endocarditis. *Am J Clin Pathol*. 1978;70:108–111.
96. Berenguer J, Sampedro I, Cercenado E, et al. Group C β-hemolytic streptococcal bacteremia. *Diagn Microbiol Infect Dis*. 1992;15:151–155.
97. Carmeli Y, Ruoff KL. Report of cases of and taxonomic considerations for large-colony-forming Lancefield group C streptococcal bacteremia. *J Clin Microbiol*. 1995;33:2114–2117.
98. Wasky KL, Kollisch N, Densen P. Group G streptococcal bacteremia: the clinical experience at Boston University Medical Center and a critical review of the literature. *Arch Intern Med*. 1985;145:58–61.
99. Rolston KVI, Chandraseker PH, LeFrock JL. Antimicrobial tolerance in group C and group G streptococci. *J Antimicrob Chemother*. 1984;13: 389–392.
100. Yin J, Yu S, Liu X, et al. Prevalence and mechanism of resistance to antimicrobial agents in group G streptococcal isolates from China. *Antimicrob Agents Chemother*. 2011;55:402–404.
101. Yang QP, Liu WP, Guo LX, et al. Autopsy report of four cases who died from *Streptococcus suis* infection, with a review of the literature. *Eur J Clin Microbiol Infect Dis*. 2009;28:447–453.
102. Mai NT, Hoa NT, Nga TV, et al. *Streptococcus suis* meningitis in adults in Vietnam. *Clin Infect Dis*. 2008;46:659–667.
103. Tan JH, Yeh BI, Seet CSR. Deafness due to haemorrhagic labyrinthitis and a review of relapses in *Streptococcus suis* meningitis. *Singapore Med J*. 2010;51:e30–e33.
104. Rizvi M, Fatima N, Shukla I, et al. *Stomatococcus mucilaginosus* meningitis in a healthy 2-month-old child. *J Med Microbiol*. 2008;57:382–383.
105. Lowry TR, Brennan JA. *Stomatococcus mucilaginosus* infection leading to early cervical necrotizing fasciitis. *Otolaryngol Head Neck Surg*. 2005;132:658–660.
106. Michels F, Colaert J, Gheysen F, et al. Late prosthetic joint infection due to *Rothia mucilaginosa*. *Acta Orthop Belg*. 2007;73:263–267.
107. Maraki S, Papadakis IS. *Rothia mucilaginosa* pneumonia: a literature review. *Infect Dis*. 2015;47:125–129.
108. Ramanan P, Barreto JN, Osmon DR, et al. *Rothia* bacteremia: a 10-year experience at Mayo Clinic, Rochester, Minnesota. *J Clin Microbiol*. 2014;52:3184–3189.
109. Suh B. Resolution of persistent *Pediococcus* bacteremia with daptomycin treatment: case report and review of the literature. *Diagn Microbiol Infect Dis*. 2010;66: 111–115.

203 *Streptococcus anginosus* Group

Cathy A. Petti and Charles W. Stratton IV

SHORT VIEW SUMMARY

Definition
- The *Streptococcus anginosus (milleri)* group comprises three distinct species: *S. anginosus, S. constellatus,* and *S. intermedius.*

Epidemiology
- Members of the *S. anginosus* group are found as part of the oropharyngeal, urogenital, and gastrointestinal microbiota. When pathogenic, these streptococci are often associated with polymicrobial abscess formation, bacteremia, and endocarditis.

Microbiology
- These microorganisms are microaerophilic, catalase-negative, gram-positive cocci and are easily identified with conventional methods. They are generally susceptible to β-lactam antibiotics but often cause polymicrobial infections with copathogens.

Diagnosis
- Depending on the clinical presentation, infections are usually diagnosed by culturing a specimen from the source of infection.

Therapy
- β-Lactam antibiotics are generally used; abscesses may require incision and drainage and antimicrobial therapy with broader coverage, such as that provided by ampicillin-sulbactam or piperacillin-tazobactam, in order to cover copathogens.

The *Streptococcus anginosus (milleri)* group is a subgroup within the viridans-group streptococci that includes three separate streptococcal species: *S. anginosus, S. constellatus,* and *S. intermedius.*[1–5] These viridans-group streptococci are part of the normal flora of the human oropharynx[6] and urogenital and gastrointestinal tracts,[7] but tend to be more virulent than other viridans streptococci and are known to cause serious infections.[1–9] Microbiologically, members of this group are recognized by their microaerobic or anaerobic growth requirements, their formation of minute colonies, and the frequent presence of a characteristic caramel-like odor.[a] This chapter defines the three species[1,2,5] and subspecies[6,16–19] currently making up the *S. anginosus* group and discusses their role in clinical infections.[2–4,7–9,12,20–24]

EPIDEMIOLOGY

Clinically, this group causes invasive pyogenic infections in both adults[b] and children,[2–4,22–24] which usually differentiates them from the other viridans-group streptococci.[2–4,19,25] Members of the *S. anginosus* group have been considered normal commensals of the human microbiota.[6,7] *S. constellatus* is usually found in the pharynx. *S. intermedius* is more commonly found in dental plaque, whereas *S. anginosus* is more frequently found in the gastrointestinal tract.[7] Spread from the gastrointestinal tract to the vagina with subsequent vaginal colonization is common.[26] Owing to a number of virulence factors, these streptococci are associated with a wide variety of infections.[2–4,7–9,12,20–24] When pathogenic, the members of the *S. anginosus (milleri)* group are characterized by their proclivity to cause abscesses and should be considered true pathogens when isolated from blood cultures or other clinically relevant cultures.

MICROBIOLOGY

S. intermedius, S. constellatus, and *S. anginosus* are three distinct species[1,2] that constitute the *S. anginosus* group.[1–5] This group is also commonly referred to as the *S. milleri* group.[3,4] Genetic and phenotypic studies[1–9,16,17,20] have clearly demonstrated that the *S. anginosus* group consists of these three distinct streptococcal species, and further subspecies of *S. constellatus* and *S. anginosus* have been identified.[6,9,16–18,20] The clinical relevance of these subspecies remains to be determined.

Molecular Subspecies

Within these three distinct streptococcal species, a number of subspecies have been recognized or proposed based primarily on molecular testing rather than phenotypic methods, the latter being highly variable.[2,6,9,16–18,20] *S. constellatus* has three subspecies: *S. constellatus* subsp. *constellatus, S. constellatus* subsp. *pharyngis,* and *S. constellatus* subsp. *viborgensis. S. anginosus* has two subspecies: *S. anginosus* subsp. *anginosus* and *S. anginosus* subsp. *whileyi.* A third genomosubspecies has tentatively been proposed for *S. anginosus*: *S. anginosus* subsp. *vellorensis.*[18] Of note is that *S. anginosus* subsp. *vellorensis* harbors superantigen and extracellular DNase coding genes identical to genes found in *Streptococcus pyogenes.*[18] The various species and subspecies appear to be associated with a number of different body habitats and sites and types of clinical infection. Microbiologically, members of this group are recognized by their microaerobic or anaerobic growth requirements, their formation of minute colonies, and the frequent presence of a characteristic caramel-like odor.[2–5,7–11,20] This chapter defines the three species and subspecies currently making up the *S. anginosus* group and discusses their role in clinical infections.

Phenotypic Characteristics

Members of the *S. anginosus* group share the phenotypic characteristics of the members of the genus *Streptococcus,* whose classification in general is based on patterns of hemolysis, Lancefield serologic antigenic reactions, growth properties, and biochemical reactions (Fig. 203.1). Like other streptococci, these organisms may be β-hemolytic, α-hemolytic, or γ-hemolytic on sheep blood agar. Members of the *S. anginosus* group often exhibit Lancefield antigens A, C, F, or G[2,5,6,11] but can be differentiated from other Lancefield-grouped streptococci by the small size (less than 0.5 mm) of their colonies. In general, β-hemolytic strains of *S. constellatus* react with Lancefield serologic group F antibody.[5,6,12,13] Strains containing the group F antigen may cross-react with the other grouping sera (Lancefield groupings) and therefore are of little value in identifying these organisms.[2,5,6,11]

Gram staining of *S. intermedius* strains reveals gram-positive spherical or ovoid cells that form short chains or pairs. *S. anginosus* group can be differentiated from other streptococci by a combination of three

[a]References 1, 2, 5, 6, 8, 10–15.
[b]References 2–4, 7–9, 16, 17, 20, 21.

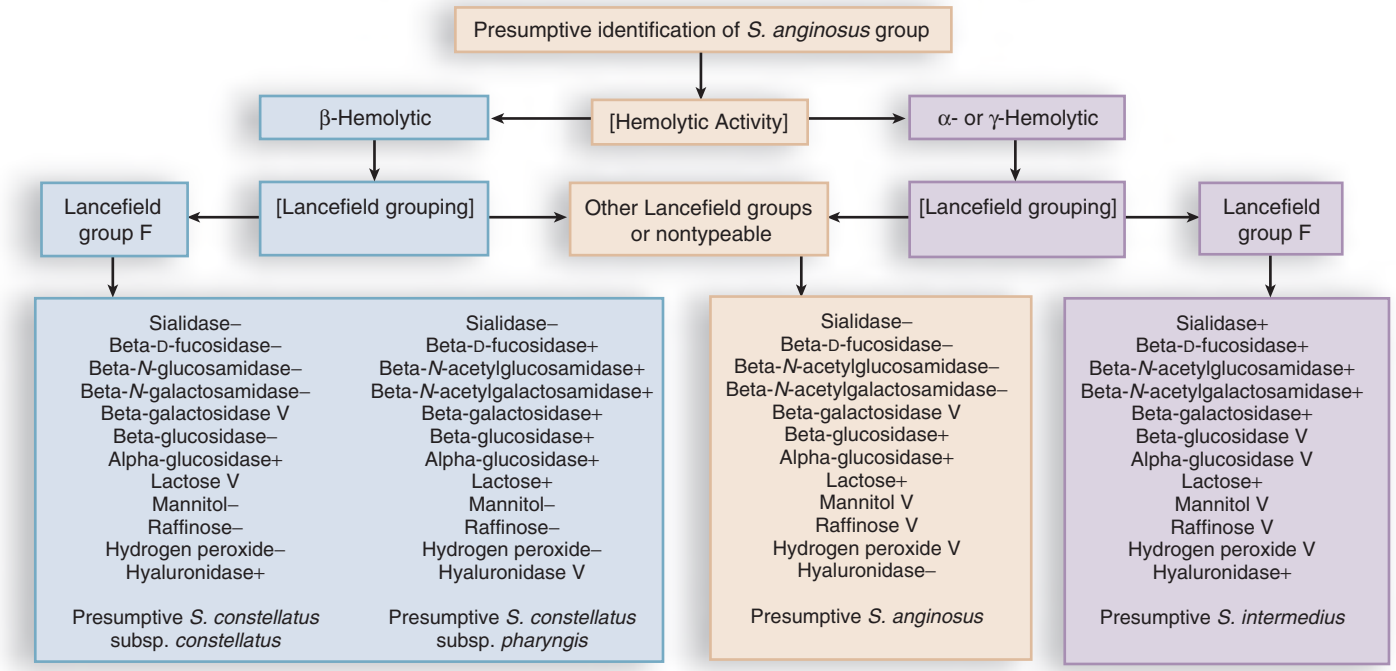

FIG. 203.1 Phenotypic differentiation of the members of the *Streptococcus anginosus* group. +, At least 90% of strains have a positive reaction; –, at least 90% of strains have a negative reaction; *V,* variable. *(Modified from Whiley RA, Fraser HY, Hardie JM, et al. Phenotypic differentiation of* Streptococcus constellatus, Streptococcus intermedius, *and* Streptococcus anginosus *[the* Streptococcus milleri *group]: association with different body sites and clinical infections.* J Clin Microbiol. *1990;28:1497–1501; and Whiley RA, Hall LMC, Hardie JM, Beighton D. A study of small colony, beta-haemolytic, Lancefield group C streptococci within the anginosus group: description of* Streptococcus constellatus *subsp.* pharyngis *subsp. nov., associated with the human throat and pharyngitis.* Int J Syst Bacteriol. *1999;49:1443–1449.)*

TABLE 203.1 Presumptive Identification of Members of the *Streptococcus anginosus* Group

Growth of Minute Streptococcal Colonies Under Microaerobic-Anaerobic Conditions
Acid from:
Insulin –
Sorbitol –
Salicin +
Hydrolysis of:
Hippurate –
Esculin +
Deoxyribonuclease –
Arginine dihydrolysis +
Voges-Proskauer test[a] +
Caramel-like odor V
↓
Presumptive *S. anginosus* group

+, ≥90% of strains have a positive reaction; –, ≥90% of strains have a negative reaction; *V,* variable.
[a]Rare exceptions.
Modified from Spellerberg B, Brandt C. Streptococcus. *In: Murray PR, Baron EJ, Jorgenson JH, et al, eds.* Manual of Clinical Microbiology. *9th ed. Washington DC: American Society for Microbiology Press; 2007:412–429; Whiley RA, Fraser HY, Hardie JM, et al. Phenotypic differentiation of* Streptococcus constellatus, Streptococcus intermedius, *and* Streptococcus anginosus *(the* Streptococcus milleri *group): association with different body sites and clinical infections.* J Clin Microbiol. *1990;28:1497–1501; and Hinnebusch CJ, Nikolai DM, Bruckner DA. Comparison of API Rapid Strep, Baxter Microscan Rapid Pos ID panel, BBL Minitek Differential Identification System, IDS RapID STR System, and Vitek GPI to conventional biochemical tests for identification of viridans streptococci.* Am J Clin Pathol. *1991;96:459–463.*

rapid tests: a positive Voges-Proskauer test for acetoin production, hydrolysis of arginine, and failure to ferment sorbitol.[2–4] In addition, the presence of the caramel-like odor, often attributed to the production of a diacetyl metabolite, can be helpful.[10,11] These characteristics are summarized in Table 203.1.

Taxonomy

The diversity of hemolytic and Lancefield groupings has made identification of these pathogens difficult in many laboratories.[2–5] Whiley and coworkers[5] have noted that almost all *S. intermedius* strains (93%) are not β-hemolytic, whereas 38% of *S. constellatus* and 12% of *S. anginosus* are β-hemolytic. Laboratories can readily differentiate the three members of the *S. anginosus* group by using phenotypic characteristics that correlate well with molecular taxonomic techniques.[2–9,16,17,20] A number of commercial systems are available for the identification of viridans streptococci, and studies have shown similar performance to manual biochemical testing.[14,15,26,27]

Molecular Diagnostic Methods

Nucleic acid amplification assays have been developed for the identification of clinically relevant viridans-group streptococci to the species and group level. Targets for these assays have included the 16S rRNA gene, the 16S-23S rRNA intergenic spacer region, *tuf* gene, *rpoB* gene, or *groEL* gene. Most assays require both amplification and sequencing of the targeted region, making the method impractical for routine use. In addition, viridans streptococci are competent—that is, they freely exchange genetic material within and between species. This phenomenon makes the taxonomic classification of viridans streptococci with DNA target sequencing and their identification to species level much more challenging. Non–sequence-based methods for identification, such as matrix-assisted laser desorption/ionization–time-of-flight (MALDI-TOF) mass spectrometry, are fast, reliable and cost-effective identification methods for *S. anginosus* group, but identification to the species level is challenging.[28,29]

PATHOGENESIS

The ability of the *S. anginosus* group to cause invasive infections and the tendency to form abscesses have long been recognized.[2–4] The pyogenic potential among the members of the *S. anginosus* group does vary considerably.[7,8,20,21,30] Although the reasons for these pathogenic

characteristics are not yet completely understood, a number of factors contribute to invasion and abscess formation.

Mixed Infections Contribute to Abscess Formation

Mixed infections involving members of the *S. anginosus* group and other microbes (e.g., *Eikenella corrodens,* Enterobacteriaceae, and anaerobes) contribute to abscess formation by allowing more rapid replication of the streptococci.[18,22,24,31–33] Murine models of pneumonia have been used to demonstrate synergy between members of the *S. anginosus* group and oral anaerobes.[31,32] These studies have found that mortality was higher, abscesses or empyema were more frequently noted on histopathologic examination, and viable bacteria were more numerous in the lungs of mice with mixed infections caused by members of the *S. intermedius* group and oral anaerobes than in the lungs of mice with monomicrobial infection. In vitro studies by these and other investigators have confirmed that anaerobes enhance the growth of *S. anginosus* group organisms.[31–33] In clinical cases in which *S. anginosus* group members cause acute pneumonia, pulmonary abscess, and/or thoracic empyema in humans, the predominant species recovered along with *S. anginosus* group isolates were anaerobic bacteria,[32,34–38] confirming the clinical importance of anaerobic copathogens in pulmonary and thoracic infections.

Virulence Factors

Anginosus group streptococci also possess virulence factors that are likely to be involved in their ability to cause serious invasive infections. For example, members of the *S. anginosus* group may express a number of different adhesins on their cell surfaces that facilitate adherence to substrates found in their natural environment.[39–46] All members of the *S. anginosus* group are able to bind fibronectin via a cell surface protein,[41] and some strains are able to bind to platelets, fibrin, fibrin clots, and fibrinogen.[43] This property is thought to be a factor in the ability of these pathogens to cause endocarditis. Fibrinogen binding may, in turn, aid in platelet aggregation, which would also facilitate the development of endocarditis.[44,45] In an experimental rat endocarditis model in which all three species of the *S. anginosus* group were studied, *S. anginosus* strains produced infective vegetations and bacteremia in almost all catheterized rats, *S. constellatus* strains did so less frequently, and *S. intermedius* strains did so only occasionally.[46] Moreover, the vegetations infected with *S. anginosus* strains harbored significantly higher numbers of microorganisms than those infected by other strains.

Cytotoxins

The production of pyrogenic exotoxins by other *Streptococcus* species is well known.[47,48] A unique cytolytic toxin specific for human cells, intermedilysin, has been described from a strain of *S. intermedius* isolated from a liver abscess.[49] In particular, intermedilysin has been noted to have a potent hemolytic effect on human erythrocytes, suggesting that this or similar exotoxins may be responsible for β-hemolysis on blood agar plates. Moreover, intermedilysin is essential for the invasion of human hepatic cells and is thus an important factor in the pathogenesis of liver abscesses.[50] The intermedilysin gene has been found only in *S. intermedius*.[51] Production of intermedilysin in *S. intermedius* isolates from deep-seated abscesses is higher than that in strains from normal habitats, suggesting that this cytolysin is a virulence factor.[51]

Hydrolytic Enzymes

Members of the *S. anginosus* group produce a wide variety of hydrolytic enzymes, including hyaluronidase, deoxyribonuclease, and chondroitin sulfatase.[18,52] These enzymes may facilitate the spread of these pathogens through tissues, play a role in microbial nutrition, and assist in liquefaction of pus. One of the most prevalent hydrolytic enzymes is hyaluronidase,[53] which has been found in pus[54] and shown to be a growth factor.[55] Another hydrolytic enzyme, chondroitin sulfatase, is produced by *S. intermedius*.[56] In addition, a novel glycosaminoglycan depolymerase isolated from *S. intermedius* acts on both chondroitin sulfate and hyaluronic acid.[57] Yet another enzyme that may play a role in pathogenesis is sialidase (neuraminidase), which is produced by *S. intermedius*.[58] Sialidase production by other bacteria is an important pathogenic feature because sialic acid is known to be a nutrient source for these microorganisms; members of the *S. anginosus* group also use sialic acid efficiently as a sole carbon source. Sialidase, therefore, may be a growth factor and may play a role in the ability of these microorganisms to proliferate in humans.

Immune Factors

A number of other possible virulence factors related to the host immune response have been identified. One such factor is an immunosuppressive and B-cell mitogenic protein (P90) that is produced by *S. intermedius*.[59] Mice treated with this protein were 50 times more susceptible to infection by *S. intermedius*. This virulence effect is thought to be mediated by stimulation of suppressor lymphocytes.

Superantigens

Another important virulence factor for members of the *S. anginosus* group in relation to the host immune response appears to be superantigens.[18,60] Superantigens are bacterial proteins that bind to major histocompatibility complex class II and T-cell receptors and cause stimulation of large numbers of T cells.[61] *Streptococcus dysgalactiae* subspecies *equisimilis* has been found to possess the superantigen genes *speM, ssa,* and *smeZ,* thought to be the result of the transfer of these genes from group A streptococci (GAS). In addition, the authors demonstrated the *smeZ* allele in *Streptococcus canis,* demonstrating the wide dissemination of GAS *smeZ* in another streptococcal species. Multilocus sequence analysis[18] and case reports of cervical necrotizing fasciitis involving *S. anginosus* group isolates[60] have suggested that it is very possible that these superantigen genes identical to those of *S. pyogenes* have also been transferred from GAS to new genomosubspecies of the *S. anginosus* group.

Resistance to Phagocytosis

The interaction of the *S. anginosus* group and human neutrophils also has been examined because of the striking propensity of these organisms to cause abscesses. A potential virulence factor is the frequent presence in members of the *S. anginosus* group of a polysaccharide capsule[11,62] that hinders phagocytosis. The ability to escape phagocytosis would allow these pathogens to replicate after arriving at and adhering to a site of tissue damage. A murine model used to investigate the pathogenicity of *S. constellatus* in pulmonary infections has demonstrated that virulent strains are less likely to be phagocytized and killed than avirulent strains, presumably because of capsular variation.[62] This study demonstrated that a virulent strain of *S. constellatus* is less likely to be killed by human neutrophils than the avirulent strains.[62] Another study has shown that members of the *S. anginosus* group stimulate less chemotaxis than *Staphylococcus aureus,* which may provide an advantage for proliferating bacteria.[63] In the latter study, members of the *S. anginosus* group survived ingestion by neutrophils better than strains of *S. aureus*.[62] These characteristics help explain the ability of members of the *S. anginosus* group to cause abscesses.

CLINICAL PRESENTATIONS

Head and Neck Infections

Members of the *S. anginosus* group were initially recovered from dental abscesses and continue to be recovered from endodontic and periapical dental abscesses, although their role, if any, in these processes is unclear.[64] The presence of members of the *S. anginosus* group in the oral cavity clearly predisposes to oral and maxillofacial infection[65] and to head and neck infection.[66] A transient bacteremia may occur with dental abscesses (or with dental procedures) and has been associated with intracranial metastatic abscesses.[67–72] Moreover, the anginosus group streptococci represented the most common microorganisms isolated in sinus-induced intracranial sepsis; *S. anginosus* group isolates have been recovered from intracranial and orbital empyemas in up to 50% of cases.[68–72] Because of the potential for metastatic spread, head and neck infections and sinusitis caused by *S. anginosus* group isolates require aggressive management.[70]

Intracranial Complications of Head and Neck Infections[67–72]

Bacteremia

Both bacteremia[73–80] and endocarditis[81–86] caused by *S. anginosus* group isolates have been well documented.[73–80] Many of these bacteremic

episodes are associated with an identifiable focus of infection—usually a deep-seated abscess in a visceral organ, implicating the gastrointestinal tract as the source.[77] Bacteremia also raises the possibility of endocarditis[81]; an echocardiogram may be indicated. Finally, viridans streptococci, including members of the *S. anginosus* group, have been recognized as an increasingly important cause of bacteremia in neutropenic cancer patients undergoing chemotherapy.[73] The primary species associated with bacteremia in one recent bacteremia study was *S. anginosus*.[79]

Consider the source and consequences of bacteremia. Bacteremia caused by members of the *S. anginosus* group should alert the clinician to initiate an appropriate investigation for the detection of a possible source and a possible suppurative metastatic focus of infection. The primary species associated with bacteremia in one recent bacteremia study was *S. anginosus.*[79]

Endocarditis

Endocarditis caused by *S. anginosus* group isolates also has been well documented.[81–86] Bacteremia by *S. anginosus* group isolates may be caused by, or may cause, bacterial endocarditis.[81,82] It is estimated that members of this group represent between 3% and 15% of streptococcal isolates from patients with endocarditis.[7,86] The propensity for suppuration of these pathogens contributes to their propensity to cause the complication of myocardial abscess or metastatic abscess,[74,75] although these complications do not occur in all patients. Endocarditis results either from an abnormal heart valve or a prosthetic heart valve, although the exact attachment mechanism is unknown. *S. anginosus* group strains have been shown to adhere to buccal epithelial cells and also to bind to fibronectin, which may contribute to their pathogenicity in endocarditis.[41,43–46]

Central Nervous System Infections

S. anginosus group organisms have a strikingly prominent association with brain abscesses and have been isolated in approximately 50% to 80% of these infections.[69,74,87] These organisms may be isolated in pure or mixed culture. In addition, these organisms have been found in culture-negative intracerebral abscesses by gene sequencing from direct specimens.[88] Factors associated with brain abscesses caused by these isolates include congenital heart defects, oral infections, sinusitis, otitis media, liver disease, and direct trauma. Although *S. intermedius* can be found in the mouth, it has been suggested that most brain abscesses caused by this pathogen originate from the intestine.[74] On rare occasions, *S. anginosus* group organisms cause meningitis; this often is preceded by trauma or purulent infection at another site.[89] Transient or persistent bacteremia often results in epidural abscesses of the spine. Rapid surgical drainage is a critical prognostic factor for effective management of these spinal cord abscesses. Of the three members, *S. intermedius* appears to be the one most commonly isolated from brain abscesses. For brain abscesses, the source of the infection should always be considered.[74,89]

Intraabdominal Infections

Given that members of the *S. anginosus* group are considered commensal organisms of the intestinal tract, it is not surprising to find these pathogens causing infections within the abdominal cavity. Such infections include liver abscesses, peritonitis, pelvic abscesses, subphrenic abscesses, appendicitis, abdominal wound infections, and cholangitis.[c] The use of antimicrobial drugs with minimal or no activity against the *S. anginosus* group for prophylaxis or therapy involving the abdominal cavity has been associated with the development of infections by these organisms.[90] Specifically, metronidazole alone or in combination with gentamicin appears to allow these bacteria to become pathogens, possibly through the suppression of competing organisms, such as *Bacteroides* species or *Fusobacterium* species. Infections caused by members of the *S. anginosus* group can be seen after abdominal surgery, particularly if prophylactic antibiotics do not cover these pathogens. The proclivity for liver abscess and bacteremia[91] and cholangitis[92] must be appreciated. Finally, *S. anginosus*[7] and *S. constellatus*[8] are the species in the *S. anginosus* group that are most frequently recovered from infections in the abdominal cavity.

If bacteremia is present, surgical sepsis should always be considered.[c]

[c]References 7, 8, 9, 20, 21, 90–93.

Thoracic Infections

The presence of *S. anginosus* group organisms in the oropharynx can lead to aspiration pneumonia followed by pulmonary complications, such as lung abscess, pleural empyema, or both.[31–38,62,94] Pulmonary complications may be related, in part, to the ability of *S. anginosus* group organisms to cross tissue planes and extend into adjacent tissues.[95] Moreover, pulmonary complications are particularly likely to occur with mixed pulmonary infections.[31–38] Predisposing factors to *S. anginosus* group pulmonary infections include male gender, previous pneumonia, alcoholism, cancer, and possibly cystic fibrosis and/or chronic obstructive pulmonary disease.[96–98] Significant morbidity and mortality (death rates of 15%–30%) have been associated with these pulmonary infections. Management of pulmonary infections caused by the *S. anginosus* group must be aggressive and often requires operative intervention.[34,35,99,100] Empyema necessitans and mediastinitis have also been reported.[101,102] *S. constellatus* and *S. anginosus* are the species of the group most frequently identified from respiratory tract infections.[7,8]

Pulmonary Complications

Pulmonary infections[31–38,95] and/or exacerbations of chronic obstructive pulmonary disease,[34,35,96–100] empyema necessitans, and mediastinitis[101,102] also may be due to these organisms. A number of other infections caused by members of the *S. anginosus* group have been reported. These include osteomyelitis,[103–105] septic arthritis,[105,106] and subcutaneous abscess or cellulitis.[107,108] Drug addicts appear to be at risk for subcutaneous abscesses caused by members of the anginosus group.[107] This risk may be related to blowing through needles or having other oral contacts with injection sites. Finally, peritonsillar abscesses involving anaerobic microorganisms mixed with *S. anginosus* group members have been described.[66]

THERAPY

Clinically, infections caused by members of the *S. anginosus* group continue to respond well to penicillin G and cephalosporins. Most of these streptococci have minimal inhibitory concentrations (MICs) to penicillin G of less than 0.125 μg/mL, with only occasional strains having MICs greater than 1.0 μg/mL.[79,109–114] As noted, streptococci are naturally competent, and the potential for penicillin and cephalosporin resistance clearly exists because of the horizontal transfer of genes among streptococci.[115] In one study, 29% of viridans streptococci overall, including members of the *S. anginosus* group, were tolerant to intermediate concentrations of penicillin G (MIC = 0.25 to 2 μg/mL), and 9% of all strains had an MIC to penicillin G greater than 4 μg/mL.[114] However, other studies report high MICs to penicillin in fewer than 2% of *S. anginosus* group isolates.[79,110–114,116,117] When penicillin resistance is seen, it is more common among *S. anginosus* and *S. intermedius* isolates. Although most strains of the *S. anginosus* group are relatively resistant to aminoglycosides, synergy with a β-lactam agent usually can be demonstrated. Therefore, the addition of an aminoglycoside to a β-lactam agent for treatment of endocarditis caused by members of the *S. anginosus* group is a reasonable practice, particularly for strains with intermediate MICs. This occasional increase in MICs to penicillin G does suggest that penicillin G combined with gentamicin may be prudent for treating endocarditis, although higher doses of penicillin or vancomycin could be used. Of the cephalosporins that are clinically available, cefepime, cefotaxime, and ceftriaxone have been noted to be superior in potency and spectrum for empirical coverage of patients at risk for streptococcal bacteremias.[110] Vancomycin and clindamycin have been useful for patients with β-lactam allergies. Moreover, resistance to erythromycin and clindamycin has been described.[112,113,116,117] Therefore, macrolides do not appear to be potent enough for empirical therapy.[116,117] Finally, abscesses often involve mixed infections, which may require anaerobic coverage, and surgical drainage.

Key References

The complete reference list is available online at Expert Consult.

1. Whiley RA, Beighton D. Emended descriptions and recognition of *Streptococcus constellatus, Streptococcus intermedius*, and *Streptococcus anginosus* as distinct species. *Int J Syst Evol Microbiol*. 1991;41:1–5.
2. Spellerberg B, Brandt C. *Streptococcus*. In: Jorgenson JH, Pfaller MA, Carrol KC, et al, eds. *Manual of Clinical Microbiology*. 11th ed. Washington, DC: American Society for Microbiology Press; 2015:383–402.
7. Whiley RA, Beighton D, Winstanley TG, et al. *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* (the *Streptococcus milleri* group): association with different body sites and clinical infections. *J Clin Microbiol*. 1992;30:243–244.
8. Claridge JE 3rd, Attori S, Musher DM, et al. *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* ("*Streptococcus milleri* group") are of different clinical importance and are not equally associated with abscess. *Clin Infect Dis*. 2001;32:1511–1515.
9. Junckerstorff RK, Robinson JO, Murray RJ. Invasive *Streptococcus anginosus* group infection—does the species predict the outcome? *Int J Infect Dis*. 2014;18:38–40.
16. Jacobs JA, Schot CS, Schouls LM. The *Streptococcus anginosus* species comprises five 16S rRNA ribogroups with different phenotypic characteristics and clinical relevance. *Int J Syst Evol Microbiol*. 2000;50(Pt 3):1073–1079.
17. Jensen A, Hoshino T, Kilian M. Taxonomy of the Anginosus group of the genus *Streptococcus* and description of *Streptococcus anginosus* subsp. *whileyi* subsp. nov. and *Streptococcus constellatus* subsp. viborgensis subsp. nov. *Int J Syst Evol Microbiol*. 2013;63(Pt 7):2506–2519.
24. Furuichi M, Horikoshi Y. Sites of infection associated with *Streptococcus anginosus* group among children. *J Infect Chemother*. 2017;pii: S1341-321X(17)30214-3.
28. Woods K, Beighton D, Klein JL. Identification of the '*Streptococcus anginosus* Group' by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry. *J Med Microbiol*. 2014;63(Pt 9):1143–1147.
32. Shinzato T, Saito A. The *Streptococcus milleri* group as a cause of pulmonary infections. *Clin Infect Dis*. 1995;21(suppl 2):S238–S243.
36. Noguchi S, Yatera K, Kawanami T, et al. The clinical features of respiratory infections caused by the *Streptococcus anginosus* group. *BMC Pulm Med*. 2015;15:133.
41. Willcox MD, Knox KW. Surface-associated properties of *Streptococcus milleri* group strains and their potential relation to pathogenesis. *J Med Microbiol*. 1990;31:259–270.
63. Wanahita A, Goldsmith EA, Musher DM, et al. Interaction between human polymorphonuclear leukocytes and *Streptococcus milleri* group bacteria. *J Infect Dis*. 2002;185:85–90.
65. Bancescu G, Lofthus B, Hofstad T, et al. Isolation and characterization of "*Streptococcus milleri*" group strains from oral and maxillofacial infections. *Adv Exp Med Biol*. 1997;418:165–167.
66. Han JK, Kerschner JE. *Streptococcus milleri*: an organism for head and neck infections and abscess. *JAMA Otolaryngol Head Neck Surg*. 2001;127:650–654.
69. Moazzam AA, Rajogopal SM, Sedghizadeh PP, et al. Intracranial bacterial infections of oral origin. *J Clin Neurosci*. 2015;22:800–806.
76. Bert F, Bariou-Lancelin M, Lanbert-Zechovsky N. Clinical significance of bacteremia involving the "*Streptococcus milleri*" group: 51 cases and review. *Clin Infect Dis*. 1998;27:385–387.
79. Wenzler E, Chandrasekaran V, Salvador P, et al. Clinical and microbiological outcomes in patients with *Streptococcus anginosus* group bacteremia identified through use of a rapid microarray assay. *J Med Microbiol*. 2015;64:1369–1374.
82. Woo PC, Tse H, Chan KM, et al. "*Streptococcus milleri*" endocarditis caused by *Streptococcus anginosus*. *Diagn Microbiol Infect Dis*. 2004;48:81–88.
86. Nilson B, Olaison L, Rasmussen M. Clinical presentation of infective endocarditis caused by different groups of non-beta haemolytic streptococci. *Eur J Clin Microbiol Infect Dis*. 2016;35:215–219.
87. Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis*. 1997;25:763–769.
88. Petti CA, Simmon KE, Bender J, et al. Culture-negative intracerebral abscesses in children and adolescents from *Streptococcus anginosus* group infection: a case series. *Clin Infect Dis*. 2008;46:1578–1580.
95. Sunwoo BY, Miller WT Jr. *Streptococcus anginosus* infections: crossing tissue planes. *Chest*. 2014;146:e121–e125.
110. Aracil B, Gomez-Garces JL, Alos JI. A study of susceptibility of 100 clinical isolates belonging to the *Streptococcus milleri* group to 16 cephalosporins. *J Antimicrob Chemother*. 1999;43:399–402.
111. Tracy M, Wanahita A, Shuhatovich Y, et al. Antibiotic susceptibilities of genetically characterized *Streptococcus milleri* group strains. *Antimicrob Agents Chemother*. 2001;45:1511–1514.
112. Yamamoto N, Kubota T, Tohyama M, et al. Trends in antimicrobial susceptibility of the *Streptococcus milleri* group. *J Infect Chemother*. 2002;8:134–137.
114. Chun S, Huh HJ, Lee NY. Species-specific difference in antimicrobial susceptibility among viridans group streptococci. *Ann Lab Med*. 2015;35:205–211.

References

1. Whiley RA, Beighton D. Emended descriptions and recognition of *Streptococcus constellatus, Streptococcus intermedius*, and *Streptococcus anginosus* as distinct species. *Int J Syst Evol Microbiol*. 1991;41:1–5.
2. Spellerberg B, Brandt C. *Streptococcus*. In: Jorgenson JH, Pfaller MA, Carrol KC, et al, eds. *Manual of Clinical Microbiology*. 11th ed. Washington, DC: American Society for Microbiology Press; 2015:383–402.
3. Ruoff KL. *Streptococcus* anginosus ("*Streptococcus milleri*"): the unrecognized pathogen. *Clin Microbiol Rev*. 1988;1:102–108.
4. Gossling J. Occurrence and pathogenicity of the *Streptococcus milleri* group. *Rev Infect Dis*. 1988;10: 257–285.
5. Whiley RA, Fraser H, Hardie JM, et al. Phenotypic differentiation of *Streptococcus intermedius, Streptococcus constellatus*, and *Streptococcus anginosus* strains within the "*Streptococcus milleri* group". *J Clin Microbiol*. 1990;28:1497–1501.
6. Whiley RA, Hall LM, Hardie JM, et al. A study of small-colony, beta-haemolytic, Lancefield group C streptococci within the Anginosus group: description of *Streptococcus constellatus* subsp. *pharyngis* subsp. nov., associated with the human throat and pharyngitis. *Int J Syst Evol Microbiol*. 1999;49(Pt 4):1443–1449.
7. Whiley RA, Beighton D, Winstanley TG, et al. *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* (the *Streptococcus milleri* group): association with different body sites and clinical infections. *J Clin Microbiol*. 1992;30:243–244.
8. Claridge JE 3rd, Attori S, Musher DM, et al. *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* ("*Streptococcus milleri* group") are of different clinical importance and are not equally associated with abscess. *Clin Infect Dis*. 2001;32:1511–1515.
9. Junckerstorff RK, Robinson JO, Murray RJ. Invasive *Streptococcus anginosus* group infection—does the species predict the outcome? *Int J Infect Dis*. 2014;18:38–40.
10. Chew TA, Smith JM. Detection of diacetyl (caramel odor) in presumptive identification of the "*Streptococcus milleri*" group. *J Clin Microbiol*. 1992;30:3028–3029.
11. Brogan O, Malone J, Fox C, et al. Lancefield grouping and smell of caramel for presumptive identification and assessment of pathogenicity in the *Streptococcus milleri* group. *J Clin Pathol*. 1997;50:332–335.
12. Shlaes DM, Lerner PI, Wolinsky E, et al. Infections due to Lancefield group F and related streptococci (*S. milleri*, *S. anginosus*). *Medicine (Baltimore)*. 1981;60:197–207.
13. Tabata A, Sato Y, Maya K, et al. A streptolysin S homologue is essential for β-haemolytic *Streptococcus constellatus* subsp. *constellatus* cytotoxicity. *Microbiology*. 2014;160(Pt 5):980–991.
14. Hinnebusch CJ, Nikolai DM, Bruckner DA. Comparison of API Rapid Strep, baxter MicroScan Rapid Pos ID panel, BBL Minitek Differential Identification System, IDS RapID STR system, and Vitek GPI to conventional biochemical tests for identification of viridans streptococci. *Am J Clin Pathol*. 1991;96:459–463.
15. Flynn CE, Ruoff KL. Identification of "*Streptococcus milleri*" group isolates to the species level with a commercially available rapid test system. *J Clin Microbiol*. 1995;33:2704–2706.
16. Jacobs JA, Schot CS, Schouls LM. The *Streptococcus anginosus* species comprises five 16S rRNA ribogroups with different phenotypic characteristics and clinical relevance. *Int J Syst Evol Microbiol*. 2000;50(Pt 3): 1073–1079.
17. Jensen A, Hoshino T, Kilian M. Taxonomy of the Anginosus group of the genus *Streptococcus* and description of *Streptococcus anginosus* subsp. *whileyi* subsp. nov. and *Streptococcus constellatus* subsp. *viborgensis* subsp. nov. *Int J Syst Evol Microbiol*. 2013;63(Pt 7):2506–2519.
18. Babbar A, Kumar VN, Bergmann R, et al. Members of a new subgroup of *Streptococcus anginosus* harbor virulence related genes previously observed in *Streptococcus pyogenes*. *Int J Med Microbiol*. 2017;307:174–181.
19. Coykendall AL. Classification and identification of the viridans streptococci. *Clin Microbiol Rev*. 1989;2:315–328.
20. Asam D, Spellerberg B. Molecular pathogenicity of *Streptococcus anginosus*. *Mol Oral Microbiol*. 2014;29:145–155.
21. Fazili T, Riddell S, Kiska D, et al. *Streptococcus anginosus* group bacterial infections. *Am J Med Sci*. 2017;354: 257–261.
22. Stelzmueller I, Fille M, Hager J, et al. Group milleri streptococci in paediatric infections. *Eur J Pediatr Surg*. 2009;19:21–24.
23. Faden HS. Infections associated with *Streptococcus intermedius* in children. *Pediatr Infect Dis J*. 2016;35: 1047–1048.
24. Furuichi M, Horikoshi Y. Sites of infection associated with *Streptococcus anginosus* group among children. *J Infect Chemother*. 2017;pii: S1341-321X(17)30214-3.
25. Doern CD, Burnham C-AD. It's not easy being green: the viridans group streptococci, with a focus on pediatric clinical manifestations. *J Clin Microbiol*. 2010;48: 3829–3835.
26. Ahmet Z, Warren M, Houang ET. Species identification of members of the *Streptococcus milleri* group isolated from the vagina by ID 32 Strep system and differential phenotypic characteristics. *J Clin Microbiol*. 1995;33:1592–1595.
27. Brigante G, Luzzaro F, Bettaccini A, et al. Use of the Phoenix automated system for identification of *Streptococcus* and *Enterococcus* spp. *J Clin Microbiol*. 2006;44:3263–3267.
28. Woods K, Beighton D, Klein JL. Identification of the '*Streptococcus anginosus* Group' by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry. *J Med Microbiol*. 2014;63(Pt 9):1143–1147.
29. Arinot-Garcia R, Pinho MD, Carrico JA, et al. Comparing matrix-assisted laser desorption ionization–time of flight mass spectrometry and phenotypic and molecular methods for identification of species within the *Streptococcus anginosus* group. *J Clin Microbiol*. 2015;53:3580–3588.
30. Kubo O, Nikola S, Geffen Y, et al. The pyogenic potential of the different *Streptococcus anginosus* group bacterial species: retrospective cohort study. *Epidemiol Infect*. 2017;145:3065–3069.
31. Shinzato T, Saito A. A mechanism of pathogenicity of "*Streptococcus milleri* group" in pulmonary infection: synergy with an anaerobe. *J Med Microbiol*. 1994;40: 118–123.
32. Shinzato T, Saito A. The *Streptococcus milleri* group as a cause of pulmonary infections. *Clin Infect Dis*. 1995;21(suppl 2):S238–S243.
33. Young KA, Allaker RP, Hardie JM, et al. Interactions between *Eikenella corrodens* and '*Streptococcus milleri*-group' organisms: possible mechanisms of pathogenicity in mixed infections. *Antonie Van Leeuwenhoek*. 1996;69:371–373.
34. Steizmueller I, Biebl M, Berger N, et al. Relevance of group milleri streptococci in thoracic surgery: a clinical update. *Am Surg*. 2007;73:492–497.
35. Tsang KY, Leung WS, Chan VL, et al. Complicated parapneumonic effusion and empyema thoracis: microbiology and predictors of adverse outcomes. *Hong Kong Med J*. 2007;13:176–186.
36. Noguchi S, Yatera K, Kawanami T, et al. The clinical features of respiratory infections caused by the *Streptococcus anginosus* group. *BMC Pulm Med*. 2015;15:133.
37. Mukae H, Noguchi S, Naito K, et al. The importance of obligate anaerobes and the *Streptococcus anginosus* group in pulmonary abscess: a clone library analysis using bronchoalveolar lavage fluid. *Respiration*. 2016;92:80–89.
38. Hirai J, Sakanashi D, Haranaga S, et al. Case-control study of pneumonia patients with *Streptococcus anginosus* group bacteria in their sputum. *J Infect Chemother*. 2016;22:794–799.
39. Jenkinson HF, Lamont FJ. Streptococcal adhesion and colonization. *Crit Rev Oral Biol Med*. 1997;8:175–200.
40. Noobs AH, Lamont RJ, Jenkinson HF. Streptococcus adherence and colonization. *Microbiol Mol Biol Rev*. 2009;73:407–450.
41. Willcox MD, Knox KW. Surface-associated properties of *Streptococcus milleri* group strains and their potential relation to pathogenesis. *J Med Microbiol*. 1990;31:259–270.
42. Willcox MD, Patrikakis M, Loo CY, et al. Albumin-binding proteins on the surface of the *Streptococcus milleri* group and characterization of the albumin receptor of *Streptococcus intermedius* C5. *J Gen Microbiol*. 1993;139:2451–2458.
43. Willcox MD, Oakley HJ, Harty DW, et al. Lancefield group C *Streptococcus milleri* group strains aggregate human platelets. *Microb Pathog*. 1994;16:451–457.
44. Willcox MD. Potential pathogenic properties of members of the "*Streptococcus milleri*" group in relation to the production of endocarditis and abscesses. *J Med Microbiol*. 1995;43:405–410.
45. Kitada K, Inoue M, Kitano M. Infective endocarditis-inducing abilities of "*Streptococcus milleri*" group. *Adv Exp Med Biol*. 1997;418:161–163.
46. Kitada K, Inoue M, Kitano M. Experimental endocarditis induction and platelet aggregation by *Streptococcus anginosus*, *Streptococcus constellatus* and *Streptococcus intermedius*. *FEMS Immunol Med Microbiol*. 1997;19:25–32.
47. Bohach GA, Stauffacher CV, Ohlendorf DH, et al. The staphylococcal and streptococcal pyrogenic toxin family. *Adv Exp Med Biol*. 1996;391:131–154.
48. Kobo O, Nikola S, Geffen Y, et al. The pyogenic potential of the different *Streptococcus anginosus* group bacterial species: retrospective cohort study. *Epidemiol Infect*. 2017;145:3065–3069.
49. Nagamune H, Ohnishi C, Katsuura A, et al. Intermedilysin. A cytotoxic toxin specific for human cells of a *Streptococcus intermedius* isolated from human liver abscess. *Adv Exp Med Biol*. 1997;418:773–775.
50. Sukeno A, Nagamune H, Whiley RA, et al. Intermedilysin is essential for the invasion of hepatoma HepG2 cells by *Streptococcus intermedius*. *Microbiol Immunol*. 2005;49: 681–694.
51. Nagamune H, Whiley RA, Goto T, et al. Distribution of the intermedilysin gene among the Anginosus group streptococci and correlation between intermedilysin production and deep-seated infection with *Streptococcus intermedius*. *J Clin Microbiol*. 2000;38:220–226.
52. Jacobs JA, Stobberingh EE. Hydrolytic enzymes of *Streptococcus anginosus*, *Streptococcus constellatus* and *Streptococcus intermedius* in relation to infection. *Eur J Clin Microbiol Infect Dis*. 1995;14:818–820.
53. Shain H, Homer KA, Aduse-Opoku J, et al. A conserved region of a hyaluronidase gene from *Streptococcus intermedius*. *Adv Exp Med Biol*. 1997;418:769–772.
54. Takao A, Nagashima H, Usui H, et al. Hyaluronidase activity in human pus from which *Streptococcus intermedius* was isolated. *Microbiol Immunol*. 1997;41:795–798.
55. Homer K, Shain H, Beighton D. The role of hyaluronidase in growth of *Streptococcus intermedius* on hylauronate. *Adv Exp Med Biol*. 1997;418:681–683.
56. Shain H, Homer KA, Beighton D. Degradation and utilisation of chondroitin sulfate by *Streptococcus intermedius*. *J Med Microbiol*. 1996;44:372–380.
57. Shain H, Homer KA, Beighton D. Purification and properties of a novel glycosaminoglycan depolymerase from *Streptococcus intermedius* strain UNS 35. *J Med Microbiol*. 1996;44:381–389.
58. Byers HL, Homer KA, Beighton D. Sialic acid utilisation by viridans streptococci. *Adv Exp Med Biol*. 1997;418: 713–716.
59. Lima M, Bandeira A, Portnoi D, et al. Protective effect of a T-cell-dependent immunosuppressive, B-cell-mitogenic protein (F3'EP-Si, or P90) produced by *Streptococcus intermedius*. *Infect Immun*. 1992;60:3571–3578.
60. Elander J, Nekludov M, Larsson A, et al. Cervical necrotizing fasciitis: descriptive, retrospective analysis of 59 cases treated at a single center. *Eur Arch Otorhinolaryngol*. 2016;273:4461–4467.
61. Fraser JD, Proft T. The bacterial superantigen and superantigen-like proteins. *Immunol Rev*. 2008;225: 226–243.
62. Toyoda K, Kusano N, Saito A. Pathogenicity of the *Streptococcus milleri* group in pulmonary infections—effect on phagocytic killing by human polymorphonuclear neutrophils. *Kansenshogaku Zasshi*. 1995;69:308–315.
63. Wanahita A, Goldsmith EA, Musher DM, et al. Interaction between human polymorphonuclear leukocytes and *Streptococcus milleri* group bacteria. *J Infect Dis*. 2002;185:85–90.
64. Sassone LM, Fidel R, Faveri M, et al. Microbiological evaluation of primary endodontic infections in teeth with and without sinus tract. *Int Endod J*. 2008;41:508–515.
65. Bancescu G, Lofthus B, Hofstad T, et al. Isolation and characterization of "*Streptococcus milleri*" group strains from oral and maxillofacial infections. *Adv Exp Med Biol*. 1997;418:165–167.
66. Han JK, Kerschner JE. *Streptococcus milleri*: an organism for head and neck infections and abscess. *JAMA Otolaryngol Head Neck Surg*. 2001;127:650–654.
67. Watkins LM, Pasternack MS, Banks M, et al. Bilateral cavernous sinus thromboses and intraorbital abscesses secondary to *Streptococcus milleri*. *Ophthalmology*. 2003;110:569–574.
68. Udaondo P, Garcia-Delpech S, Diaz-Llopis M, et al. Bilateral intraorbital abscesses and cavernous sinus thromboses secondary to *Streptococcus milleri* with a favorable outcome. *Ophthal Plast Reconstr Surg*. 2008;24:408–410.
69. Moazzam AA, Rajogopal SM, Sedghizadeh PP, et al. Intracranial bacterial infections of oral origin. *J Clin Neurosci*. 2015;22:800–806.
70. Jones RL, Violaris NS, Chavda SV, et al. Intracranial complications of sinusitis: the need for aggressive management. *J Laryngol Otol*. 1995;109:1061–1062.
71. Greenlee JE. Subdural empyema. *Curr Treat Options Neurol*. 2003;5:13–22.
72. Deutschmann MW, Livingstone D, Cho JJ, et al. The significance of *Streptococcus anginosus* group in intracranial complications of pediatric rhinosinusitis. *JAMA Otolarynol Head Neck Surg*. 2013;139:157–160.

73. Awada A, van der Auwera P, Meunier F, et al. Streptococcal and enterococcal bacteremia in patients with cancer. *Clin Infect Dis*. 1992;15:33–48.
74. Casariego E, Rodriguez A, Corredoira JC, et al. Prospective study of *Streptococcus milleri* bacteremia. *Eur J Clin Microbiol Infect Dis*. 1996;15:194–200.
75. Salavert M, Gomez L, Rodriguez-Carballeira M, et al. Seven-year review of bacteremia caused by *Streptococcus milleri* and other viridans streptococci. *Eur J Clin Microbiol Infect Dis*. 1996;15:365–371.
76. Bert F, Bariou-Lancelin M, Lanbert-Zechovsky N. Clinical significance of bacteremia involving the "*Streptococcus milleri*" group: 51 cases and review. *Clin Infect Dis*. 1998;27:385–387.
77. Steizmueller I, Pfausler B, File M, et al. *Streptococcus milleri* group isolates from blood cultures: consider surgical sepsis. *Surg Infect (Larchmt)*. 2009;10:259–263.
78. Giuliano S, Rubini G, Conte A, et al. *Streptococcus anginosus* group disseminated infection: case report and review of literature. *Infez Med*. 2012;20:145–154.
79. Wenzler E, Chandrasekaran V, Salvador P, et al. Clinical and microbiological outcomes in patients with *Streptococcus anginosus* group bacteremia identified through use of a rapid microarray assay. *J Med Microbiol*. 2015;64:1369–1374.
80. Suzuki H, Hase R, Otsuka Y, et al. Bloodstream infections caused by *Streptococcus anginosus* group bacteria: a retrospective analysis of 78 cases at a Japanese tertiary hospital. *J Infect Chemother*. 2016;22:456–460.
81. Lefort A, Lortholary O, Casassus P, et al. Comparison between adult endocarditis due to beta-hemolytic streptococci (serogroups a, B, C, and G) and *Streptococcus milleri*: a multicenter study in France. *Arch Intern Med*. 2002;162:2450–2456.
82. Woo PC, Tse H, Chan KM, et al. "*Streptococcus milleri*" endocarditis caused by *Streptococcus anginosus*. *Diagn Microbiol Infect Dis*. 2004;48:81–88.
83. Rashid RM, Salah W, Parada JP. '*Streptococcus milleri*' aortic valve endocarditis and hepatic abscess. *J Med Microbiol*. 2007;56(Pt 2):280–282.
84. Tran MP, Caldwell-McMillan M, Khalife W, et al. *Streptococcus intermedius* causing infective endocarditis and abscesses; a report of three cases and review of the literature. *BMC Infect Dis*. 2008;8:154.
85. Elhussein TA, Hutchison SJ. *Streptococcus constellatus* community acquired pneumonia with subsequent isolated pulmonic valve endocarditis and abscess formation in a structurally normal heart. *J Cardiovasc Ultrasound*. 2014;22:91–94.
86. Nilson B, Olaison L, Rasmussen M. Clinical presentation of infective endocarditis caused by different groups of non-beta haemolytic streptococci. *Eur J Clin Microbiol Infect Dis*. 2016;35:215–219.
87. Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis*. 1997;25:763–769.
88. Petti CA, Simmon KE, Bender J, et al. Culture-negative intracerebral abscesses in children and adolescents from *Streptococcus anginosus* group infection: a case series. *Clin Infect Dis*. 2008;46:1578–1580.
89. Cabellos C, Viladrich PF, Corredoira J, et al. Streptococcal meningitis in adult patients: current epidemiology and clinical spectrum. *Clin Infect Dis*. 1999;28:1104–1108.
90. Tresadern JC, Farrand RJ, Irving MH. *Streptococcus milleri* and surgical sepsis. *Ann R Coll Surg Engl*. 1983;65:78–79.
91. Corredoira J, Casariego E, Moreno C, et al. Prospective study of *Streptococcus milleri* hepatic abscess. *Eur J Clin Microbiol Infect Dis*. 1998;17:556–560.
92. Molina JM, Leport C, Bure A, et al. Clinical and bacterial features of infections caused by *Streptococcus milleri*. *Scand J Infect Dis*. 1991;23:659–666.
93. Hardwick RH, Taylor A, Thompson MH, et al. Association between *Streptococcus milleri* and abscess formation after appendicitis. *Ann R Coll Surg Engl*. 2000;81:24–26.
94. Wong CA, Donald F, Macfarlane JT. *Streptococcus milleri* pulmonary disease: a review and clinical description of 25 patients. *Thorax*. 1995;50:1093–1096.
95. Sunwoo BY, Miller WT Jr. *Streptococcus anginosus* infections: crossing tissue planes. *Chest*. 2014;146: e121–e125.
96. Parkins MD, Sibley CD, Surette MG, et al. The *Streptococcus milleri* group—an unrecognized cause of disease in cystic fibrosis: a case series and literature review. *Pediatr Pulmonol*. 2008;43:490–497.
97. Grinwis ME, Sibley CD, Parkins MD, et al. Characterization of *Streptococcus milleri* isolates from expectorated sputum of adult patients with cystic fibrosis. *J Clin Microbiol*. 2010;48:395–401.
98. Navratilova L, Bardon J, Novotny R, et al. The *Streptococcus milleri* group in chronic obstructive pulmonary disease. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2016;160:378–384.
99. Prota G, Rodriguez-Caballeira M, Gomez L, et al. Thoracic infection caused by *Steptococcus milleri*. *Eur Respir J*. 1998;12:357–362.
100. Ripley RT, Cothren CC, Moore EE, et al. *Streptococcus milleri* infections of the pleural space: operative management predominates. *Am J Surg*. 2006;192: 817–821.
101. Marinella MA, Harrington GD, Standiford TJ. Empyema necessitans due to *Streptococcus milleri*. *Clin Infect Dis*. 1996;23:203–204.
102. Shishido H, Watanabe K, Matsumoto K, et al. Primary purulent mediastinitis due to *Streptococcus milleri*. *Respiration*. 1997;64:313–315.
103. Calza L, Manfredi R, Briganti E, et al. Iliac osteomyelitis and gluteal muscle abscess caused by *Streptococcus intermedius*. *J Med Microbiol*. 2001;50:480–482.
104. Griffin AT, Timbrook T, Harting J, et al. *Streptococcus anginosus* group and osteomyelitis: a single centre clinical experience. *Postgrad Med J*. 2013;89:262–265.
105. Seng P, Vernier M, Gay A, et al. Clinical features and outcomes of bone and joint infections with streptococcal involvement: 5-year experience of interregional reference centres in the South of France. *New Microbes New Infect*. 2016;12:8–17.
106. Ortel TL, Kallianos J, Gallis HA. Group C streptococcal arthritis: case report and review. *Rev Infect Dis*. 1990;12:829–837.
107. Stocker E, Cortes E, Pema K, et al. *Streptococcus milleri* as a cause of antecubital abscess and bacteremia in intravenous drug abusers. *South Med J*. 1994;87:95–96.
108. Edmiston CE Jr, Walker AP, Krepel CJ, et al. *Streptococcus milleri* group (*Streptococcus anginosus*): recovery from intra-abdominal and soft tissue sites. *Ann Clin Lab Sci*. 1991;21:56–61.
109. Limia A, Jimenez ML, Alarcon T, et al. Five-year analysis of antimicrobial susceptibility of the *Streptococcus milleri* group. *Eur J Clin Microbiol Infect Dis*. 1999;18:440–444.
110. Aracil B, Gomez-Garces JL, Alos JI. A study of susceptibility of 100 clinical isolates belonging to the *Streptococcus milleri* group to 16 cephalosporins. *J Antimicrob Chemother*. 1999;43:399–402.
111. Tracy M, Wanahita A, Shuhatovich Y, et al. Antibiotic susceptibilities of genetically characterized *Streptococcus milleri* group strains. *Antimicrob Agents Chemother*. 2001;45:1511–1514.
112. Yamamoto N, Kubota T, Tohyama M, et al. Trends in antimicrobial susceptibility of the *Streptococcus milleri* group. *J Infect Chemother*. 2002;8:134–137.
113. Chang YC, Lo HH. Identification, clinical aspects, susceptibility pattern, and molecular epidemiology of group G *Streptococcus anginosus* group isolates from central Taiwan. *Diagn Microbiol Infect Dis*. 2013;76: 262–265.
114. Chun S, Huh HJ, Lee NY. Species-specific difference in antimicrobial susceptibility among viridans group streptococci. *Ann Lab Med*. 2015;35:205–211.
115. Dowson CG, Barcus V, King S, et al. Horizontal gene transfer and the evolution of resistance and virulence determinants in *Streptococcus*. *Soc Appl Bacteriol Symp Ser*. 1997;26:S42–S51.
116. Jacobs JA, van Baar GJ, London NH, et al. Prevalence of macrolide resistance genes in clinical isolates of the *Streptococcus anginosus* ("*S. milleri*") group. *Antimicrob Agents Chemother*. 2001;45:2375–2377.
117. Asmah N, Eberspacher B, Regnath T, et al. Prevalence of erythromycin and clindamycin resistance among clinical isolates of the *Streptococcus anginosus* group in Germany. *J Med Microbiol*. 2009;58(Pt 2):222–227.