255. Butto A, Rossano JW, Nandi D, et al. Elevated troponin in the first 72 h of hospitalization for pediatric viral myocarditis is associated with ECMO: an analysis of the PHIS+ database. Pediatr Cardiol. 2018.
256. Karjalainen J, Heikkila J. "Acute pericarditis": myocardial enzyme release as evidence for myocarditis. *Am Heart J*. 1986;111:546–552.
257. Magnani JW, Danik HJ, Dec GW Jr, et al. Survival in biopsy-proven myocarditis: a long-term retrospective analysis of the histopathologic, clinical, and hemodynamic predictors. *Am Heart J*. 2006;151:463–470.
258. Morgera T, Di Lenarda A, Dreas L, et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. *Am Heart J*. 1992;124:455–467.
259. Skouri HN, Dec GW, Friedrich MG, et al. Noninvasive imaging in myocarditis. *J Am Coll Cardiol*. 2006;48:2085–2093.
260. Felker GM, Boehmer JP, Hruban RH, et al. Echocardiographic findings in fulminant and acute myocarditis. *J Am Coll Cardiol*. 2000;36:227–232.
261. Mendes LA, Dec GW, Picard MH, et al. Right ventricular dysfunction: an independent predictor of adverse outcome in patients with myocarditis. *Am Heart J*. 1994;128:301–307.
262. Abdel-Aty H, Boye P, Zagrosek A, et al. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. *J Am Coll Cardiol*. 2005;45:1815–1822.
263. Aletras AH, Kellman P, Derbyshire JA, et al. ACUT2E TSE-SSFP: a hybrid method for T2-weighted imaging of edema in the heart. *Magn Reson Med*. 2008;59:229–235.
264. Friedrich MG, Strohm O, Schulz-Menger J, et al. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. *Circulation*. 1998;97:1802–1809.
265. Gutberlet M, Spors B, Thoma T, et al. Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. *Radiology*. 2008;246:401–409.
266. Roditi GH, Hartnell GG, Cohen MC. MRI changes in myocarditis—evaluation with spin echo, cine MR angiography and contrast enhanced spin echo imaging. *Clin Radiol*. 2000;55:752–758.
267. Mahrholdt H, Goedecke C, Wagner A, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation*. 2004;109:1250–1258.
268. Laissy JP, Hyafil F, Feldman LJ, et al. Differentiating acute myocardial infarction from myocarditis: diagnostic value of early- and delayed-perfusion cardiac MR imaging. *Radiology*. 2005;237:75–82.
269. Ingkanisorn WP, Paterson DI, Calvo KR, et al. Cardiac magnetic resonance appearance of myocarditis caused by high dose IL-2: similarities to community-acquired myocarditis. *J Cardiovasc Magn Reson*. 2006;8:353–360.
270. Mahrholdt H, Wagner A, Deluigi CC, et al. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. *Circulation*. 2006;114:1581–1590.
271. Codreanu A, Djaballah W, Angioi M, et al. Detection of myocarditis by contrast-enhanced MRI in patients presenting with acute coronary syndrome but no coronary stenosis. *J Magn Reson Imaging*. 2007;25:957–964.
272. Grun S, Schumm J, Greulich S, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol*. 2012;59:1604–1615.
273. Lurz P, Eitel I, Adam J, et al. Diagnostic performance of CMR imaging compared with EMB in patients with suspected myocarditis. *JACC Cardiovasc Imaging*. 2012;5:513–524.
274. Lurz P, Luecke C, Eitel I, et al. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-trial. *J Am Coll Cardiol*. 2016;67:1800–1811.
275. Luetkens JA, Homsi R, Sprinkart AM, et al. Incremental value of quantitative CMR including parametric mapping for the diagnosis of acute myocarditis. *Eur Heart J Cardiovasc Imaging*. 2016;17:154–161.
276. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol*. 1987;1:3–14.
277. Chow LH, Radio SJ, Sears TD, et al. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. *J Am Coll Cardiol*. 1989;14:915–920.
278. Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. *Mayo Clin Proc*. 1989;64:1235–1245.
279. Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. *Circulation*. 2008;118:639–648.
280. Maisch B, Portig I, Ristic A, et al. Definition of inflammatory cardiomyopathy (myocarditis): on the way to consensus. A status report. *Herz*. 2000;25:200–209.
281. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *J Am Coll Cardiol*. 2007;50:1914–1931.
282. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34:2636–2648.
283. Chow LC, Dittrich HC, Shabetai R. Endomyocardial biopsy in patients with unexplained congestive heart failure. *Ann Intern Med*. 1988;109:535–539.
284. Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol*. 1992;19:43–47.
285. Liu P, Baughman KL. Myocarditis. In: Bonow RO, Mann DL, Zipes DP, et al, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 9th ed. Philadelphia: Saunders; 2012:1595–1610.
286. Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. *Circulation*. 2013;128:1531–1541.
287. Hyypia T. Etiological diagnosis of viral heart disease. *Scand J Infect Dis Suppl*. 1993;88:25–31.
288. Bowles NE, Vallejo J. Viral causes of cardiac inflammation. *Curr Opin Cardiol*. 2003;18:182–188.
289. Weinstein C, Fenoglio JJ. Myocarditis. *Hum Pathol*. 1987;18:613–618.
290. Easton AJ, Eglin RP. The detection of coxsackievirus RNA in cardiac tissue by in situ hybridization. *J Gen Virol*. 1988;69:285–291.
291. Weiss LM, Liu XF, Chang KL, et al. Detection of enteroviral RNA in idiopathic dilated cardiomyopathy and other human cardiac tissues. *J Clin Invest*. 1992;90:156–159.
292. Keeling PJ, Tracy S. Link between enteroviruses and dilated cardiomyopathy: serological and molecular data. *Br Heart J*. 1994;72:25–29.
293. Schwaiger A, Umlauft F, Weyrer K, et al. Detection of enteroviral ribonucleic acid in myocardial biopsies from patients with idiopathic dilated cardiomyopathy by polymerase chain reaction. *Am Heart J*. 1993;126:406–410.
294. Wheeler DS, Kooy NW. A formidable challenge: the diagnosis and treatment of viral myocarditis in children. *Crit Care Clin*. 2003;19:365–391.
295. Tracy S, Wiegand V, McManus B, et al. Molecular approaches to enteroviral diagnosis in idiopathic cardiomyopathy and myocarditis. *J Am Coll Cardiol*. 1990;15:1688–1694.
296. Why HJ, Meany BT, Richardson PJ, et al. Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy. *Circulation*. 1994;89:2582–2589.
297. Schonian U, Crombach M, Maisch B. Assessment of cytomegalovirus DNA and protein expression in patients with myocarditis. *Clin Immunol Immunopathol*. 1993;68:229–233.
298. Schenk T, Enders M, Pollak S, et al. High prevalence of human parvovirus B19 DNA in myocardial autopsy samples from subjects without myocarditis or dilative cardiomyopathy. *J Clin Microbiol*. 2009;47:106–110.
299. Lindner J, Noutsias M, Lassner D, et al. Adaptive immune responses against parvovirus B19 in patients with myocardial disease. *J Clin Virol*. 2009;44:27–32.
300. Corcioli F, Zakrzewska K, Rinieri A, et al. Tissue persistence of parvovirus B19 genotypes in asymptomatic persons. *J Med Virol*. 2008;80:2005–2011.
301. Wessely R, Klingel K, Santana LF, et al. Transgenic expression of replication-restricted enteroviral genomes in heart muscle induces defective excitation-contraction coupling and dilated cardiomyopathy. *J Clin Invest*. 1998;102:1444–1453.
302. Figulla HR, Stille-Siegener M, Mall G, et al. Myocardial enterovirus infection with left ventricular dysfunction: a benign disease compared with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 1995;25:1170–1175.
303. Martino TA, Liu P, Sole MJ. Viral infection and the pathogenesis of dilated cardiomyopathy. *Circ Res*. 1994;74:182–188.
304. Nguyen Y, Renois F, Leveque N, et al. Virus detection and semiquantitation in explanted heart tissues of idiopathic dilated cardiomyopathy adult patients by use of PCR coupled with mass spectrometry analysis. *J Clin Microbiol*. 2013;51:2288–2294.
305. Charron P, Elliott PM, Gimeno JR, et al. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. European heart journal. 2018.
306. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71:1755–1764.
307. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375:1749–1755.
308. Remes J, Helin M, Vaino P, et al. Clinical outcome and left ventricular function 23 years after acute coxsackie virus myopericarditis. *Eur Heart J*. 1990;11:182–188.
309. Lee KJ, McCrindle BW, Bohn DJ, et al. Clinical outcomes of acute myocarditis in childhood. *Heart*. 1999;82:226–233.
310. Hayakawa M, Inoh T, Yokota Y, et al. A long-term follow-up study of acute viral and idiopathic myocarditis. *Jpn Circ J*. 1983;47:1304–1309.
311. Tominaga M, Matsumori A, Okada I, et al. Beta-blocker treatment of dilated cardiomyopathy. Beneficial effect of carteolol in mice. *Circulation*. 1991;83:2021–2028.
312. Matsumori A, Igata H, Ono K, et al. High doses of digitalis increase the myocardial production of proinflammatory cytokines and worsen myocardial injury in viral myocarditis: a possible mechanism of digitalis toxicity. *Jpn Circ J*. 1999;63:934–940.
313. Leon JS, Wang K, Engman DM. Captopril ameliorates myocarditis in acute experimental Chagas' disease. *Circulation*. 2003;107:2264–2269.
314. Factor SM, Minase T, Cho S, et al. Microvascular spasm in the cardiomyopathic Syrian hamster: a preventable cause of focal myocardial necrosis. *Circulation*. 1982;66:342–354.
315. Morris SA, Weiss LM, Factor S, et al. Verapamil ameliorates clinical, pathologic and biochemical manifestations of experimental chagasic cardiomyopathy in mice. *J Am Coll Cardiol*. 1989;14:782–789.
316. Wang WZ, Matsumori A, Yamada T, et al. Beneficial effects of amlodipine in a murine model of congestive heart failure induced by viral myocarditis. A possible mechanism through inhibition of nitric oxide production. *Circulation*. 1997;95:245–251.
317. McCarthy RE, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med*. 2000;342:690–695.
318. Maybaum S, Stockwell P, Naka Y, et al. Assessment of myocardial recovery in a patient with acute myocarditis supported with a left ventricular assist device: a case report. *J Heart Lung Transplant*. 2003;22:202–209.
319. Ghelani SJ, Spaeder MC, Pastor W, et al. Demographics, trends, and outcomes in pediatric acute myocarditis in the United States, 2006 to 2011. *Circ Cardiovasc Qual Outcomes*. 2012;5:622–627.
320. Rezkalla SH, Raikar S, Kloner RA. Treatment of viral myocarditis with focus on captopril. *Am J Cardiol*. 1996;77:634–637.
321. Vallejo J, Mann DL. Antiinflammatory therapy in myocarditis. *Curr Opin Cardiol*. 2003;18:189–193.
322. Costanzo-Nordin MR, Reap EA, O'Connell JB, et al. A nonsteroid anti-inflammatory drug exacerbates Coxsackie B3 murine myocarditis. *J Am Coll Cardiol*. 1985;6:1078–1082.
323. Kilbourne ED, Wilson CB, Perrier D. The induction of gross myocardial lesions by a Coxsackie (pleurodynia) virus and cortisone. *J Clin Invest*. 1956;35:362–370.
324. Tomioka N, Kishimoto C, Matsumori A, et al. Effects of prednisolone on acute viral myocarditis in mice. *J Am Coll Cardiol*. 1986;7:868–872.
325. Ettinger J, Feucht H, Gartner R, et al. Cyclosporine A (CyA) for successful treatment of myocarditis. *Eur Heart J*. 1986;7:452.
326. Chan KY, Iwahara M, Benson LN, et al. Immunosuppressive therapy in the management of acute myocarditis in children: a clinical trial. *J Am Coll Cardiol*. 1991;17:458–460.
327. O'Connell JB, Robinson JA, Henkin RE, et al. Immunosuppressive therapy in patients with congestive cardiomyopathy and myocardial uptake of gallium-67. *Circulation*. 1981;64:780–786.

328. Anandasabapathy S, Frishman WH. Innovative drug treatments for viral and autoimmune myocarditis. *J Clin Pharmacol*. 1998;38:295–308.
329. Camargo PR, Snitcowsky R, da Luz PL, et al. Favorable effects of immunosuppressive therapy in children with dilated cardiomyopathy and active myocarditis. *Pediatr Cardiol*. 1995;16:61–68.
330. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med*. 1995;333:269–275.
331. McKenna WJ, Davies MJ. Immunosuppression for myocarditis. *N Engl J Med*. 1995;333:312–313.
332. Garg A, Shiau J, Guyatt G. The ineffectiveness of immunosuppressive therapy in lymphocytic myocarditis: an overview. *Ann Intern Med*. 1998;129:317–322.
333. Frustaci A, Chimenti C, Calabrese F, et al. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation*. 2003;107:857–863.
334. Cooper LT Jr, Hare JM, Tazelaar HD, et al. Usefulness of immunosuppression for giant cell myocarditis. *Am J Cardiol*. 2008;102:1535–1539.
335. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J*. 2009;30:1995–2002.
336. Takada H, Kishimoto C, Hiraoka Y. Therapy with immunoglobulin suppresses myocarditis in a murine coxsackievirus B3 model. Antiviral and anti-inflammatory effects. *Circulation*. 1995;92:1604–1611.
337. Kishimoto C, Takada H, Kawamata H, et al. Immunoglobulin treatment prevents congestive heart failure in murine encephalomyocarditis viral myocarditis associated with reduction of inflammatory cytokines. *J Pharmacol Exp Ther*. 2001;299:645–651.
338. Maisch B, Herzum M, Hufnagel G, et al. Immunosuppressive and immunomodulatory treatment for myocarditis. *Curr Opin Cardiol*. 1996;11:310–324.
339. Dennert R, Velthuis S, Schalla S, et al. Intravenous immunoglobulin therapy for patients with idiopathic cardiomyopathy and endomyocardial biopsy-proven high PVB19 viral load. *Antivir Ther*. 2010;15:193–201.
340. McNamara DM, Rosenblum WD, Janosko KM, et al. Intravenous immune globulin in the therapy of myocarditis and acute cardiomyopathy. *Circulation*. 1997;95:2476–2478.
341. McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation*. 2001;103:2254–2259.
342. Robinson JL, Hartling L, Crumley E, et al. A systematic review of intravenous gamma globulin for therapy of acute myocarditis. *BMC Cardiovasc Disord*. 2005;5:12.
343. Kishimoto C, Crumpacker CS, Abelmann WH. Prevention of murine coxsackie B3 viral myocarditis and associated lymphoid organ atrophy with recombinant human leucocyte interferon alpha A/D. *Cardiovasc Res*. 1988;22:732–738.
344. Wang YX, da Cunha V, Vincelette J, et al. Antiviral and myocyte protective effects of murine interferon-beta and -α2 in coxsackievirus B3-induced myocarditis and epicarditis in Balb/c mice. *Am J Physiol Heart Circ Physiol*. 2007;293:H69–H76.
345. Kuhl U, Pauschinger M, Schwimmbeck PL, et al. Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. *Circulation*. 2003;107:2793–2798.
346. Daliento L, Calabrese F, Tona F, et al. Successful treatment of enterovirus-induced myocarditis with interferon-alpha. *J Heart Lung Transplant*. 2003;22:214–217.
347. Miric M, Miskovic A, Brkic S, et al. Long-term follow-up of patients with myocarditis and idiopathic dilated cardiomyopathy after immunomodulatory therapy. *FEMS Immunol Med Microbiol*. 1994;10:65–74.
348. Matsumori A. The use of cytokine inhibitors. A new therapeutic insight into heart failure. *Int J Cardiol*. 1997;62(suppl 1):S3–S12.
349. Schultheiss HP, Piper C, Sowade K. The effect of subcutaneous treatment with interferon-beta-1b over 24 weeks on safety, virus elimination, and clinical outcome in patients with chronic viral cardiomyopathy [abstract]. *Circulation*. 2008;118:3322.
350. Kuhl U, Lassner D, von Schlippenbach J, et al. Interferon-beta improves survival in enterovirus-associated cardiomyopathy. *J Am Coll Cardiol*. 2012;60:1295–1296.
351. Felix SB, Staudt A, Landsberger M, et al. Removal of cardiodepressant antibodies in dilated cardiomyopathy by immunoadsorption. *J Am Coll Cardiol*. 2002;39:646–652.
352. Felix SB, Staudt A, Dorffel WV, et al. Hemodynamic effects of immunoadsorption and subsequent immunoglobulin substitution in dilated cardiomyopathy: three-month results from a randomized study. *J Am Coll Cardiol*. 2000;35:1590–1598.
353. Doesch AO, Konstandin M, Celik S, et al. Effects of protein A immunoadsorption in patients with advanced chronic dilated cardiomyopathy. *J Clin Apher*. 2009;24:141–149.
354. Doesch AO, Mueller S, Konstandin M, et al. Effects of protein A immunoadsorption in patients with chronic dilated cardiomyopathy. *J Clin Apher*. 2010;25:315–322.
355. Bulut D, Scheeler M, Wichmann T, et al. Effect of protein A immunoadsorption on T cell activation in patients with inflammatory dilated cardiomyopathy. *Clin Res Cardiol*. 2010;99:633–638.
356. McCormack JG, Bowler SD, Donnelly JE, et al. Successful treatment of severe cytomegalovirus infection with ganciclovir in an immunocompetent host. *Clin Infect Dis*. 1998;26:1007–1008.
357. Rotbart HA, O'Connell JF, McKinlay MA. Treatment of human enterovirus infections. *Antiviral Res*. 1998;38:1–14.
358. Rotbart HA, Webster AD. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis*. 2001;32:228–235.
359. Schiff GM, McKinlay MA, Sherwood JR. Oral efficacy of VP63843 in coxsackie-virus A21-infected volunteers [abstract H-43]. Program and Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy (New Orleans). Washington, DC: American Society for Microbiology; 1996.
360. Woods MG, Diana GD, Rogge MC, et al. In vitro and in vivo activities of WIN 54954, a new broad-spectrum antipicornavirus drug. *Antimicrob Agents Chemother*. 1989;33:2069–2074.
361. Pauksen K, Ilback NG, Friman G, et al. Therapy of coxsackie virus B3-induced myocarditis with WIN 54954 in different formulations. *Scand J Infect Dis Suppl*. 1993;88:125–130.
362. See DM, Tilles JG. Treatment of Coxsackievirus A9 myocarditis in mice with WIN 54954. *Antimicrob Agents Chemother*. 1992;36:425–428.
363. Fohlman J, Pauksen K, Hyypia T, et al. Antiviral treatment with WIN 54 954 reduces mortality in murine coxsackievirus B3 myocarditis. *Circulation*. 1996;94:2254–2259.
364. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131.
365. Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the AIRTRIP randomized clinical trial. *JAMA*. 2016;316:1906–1912.
366. Assistance Publique–Hôpitaux de Paris. Anakinra Versus Placebo for the Treatment of Acute MyocarditIS (ARAMIS). June 15, 2017. https://clinicaltrials.gov/ct2/show/NCT03018834.
367. Tilles JG, Elson SH, Shaka JA, et al. Effects of exercise on Coxsackie a9 myocarditis in adult mice. *Proc Soc Exp Biol Med*. 1964;117:777–782.
368. Damm S, Andersson LG, Henriksen E, et al. Wall motion abnormalities in male elite orienteers are aggravated by exercise. *Clin Physiol*. 1999;19:121–126.
369. Peng T, Li Y, Yang Y, et al. Characterization of enterovirus isolates from patients with heart muscle disease in a selenium-deficient area of China. *J Clin Microbiol*. 2000;38:3538–3543.
370. Kuntz J, Crane B, Weinmann S, et al; Vaccine Safety Datalink Investigator Team. Myocarditis and pericarditis are rare following live viral vaccinations in adults. *Vaccine*. 2018;36:1524–1527.
371. Seferovic PM, Ristic AD, Maksimovic R, et al. Pericardial syndromes: an update after the ESC guidelines 2004. *Heart Fail Rev*. 2013;18:255–266.
372. Osler W. Chronic cyanosis, with polycythaemia and enlarged spleen: a new clinical entity. 1903. *Am J Med Sci*. 2008;335:411–417.
373. Klacsmann PG, Bulkley BH, Hutchins GM. The changed spectrum of purulent pericarditis: an 86 year autopsy experience in 200 patients. *Am J Med*. 1977;63:666–673.
374. Sagristà-Sauleda J, Barrabes JA, Permanyer-Miralda G, et al. Purulent pericarditis: review of a 20-year experience in a general hospital. *J Am Coll Cardiol*. 1993;22:1661–1665.
375. Park S, Bayer AS. Purulent pericarditis. *Curr Clin Top Infect Dis*. 1992;12:56–82.
376. Gould K, Barnett JA, Sanford JP. Purulent pericarditis in the antibiotic era. *Arch Intern Med*. 1974;134:923–927.
377. Ilan Y, Oren R, Ben-Chetrit E. Acute pericarditis: etiology, treatment and prognosis. A study of 115 patients. *Jpn Heart J*. 1991;32:315–321.
378. Sagristà-Sauleda J, Angel J, Sanchez A, et al. Effusive-constrictive pericarditis. *N Engl J Med*. 2004;350:469–475.
379. Levy P-Y, Corey R, Berger P, et al. Etiologic diagnosis of 204 pericardial effusions. *Medicine (Baltimore)*. 2003;82:385–391.
380. Soler-Soler J, Permanyer-Miralda G, Sagrista-Sauleda J. A systematic diagnostic approach to primary acute pericardial disease. The Barcelona experience. *Cardiol Clin*. 1990;8:609–620.
381. Maisch B, Ristic AD. The classification of pericardial disease in the age of modern medicine. *Curr Cardiol Rep*. 2002;4:13–21.
382. Johnson RT, Portnoy B, Rogers NG, et al. Acute benign pericarditis. Virologic study of 34 patients. *Arch Intern Med*. 1961;108:823–832.
383. Kagan H, Bernkopf H. Pericarditis caused by Coxsackie virus B. *Ann Paediatr*. 1957;189:44–50.
384. Brodie HR, Marchessault V. Acute benign pericarditis caused by Coxsackie virus group B. *N Engl J Med*. 1960;262:1278–1280.
385. Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. *JAMA*. 2015;314:1498–1506.
386. Imazio M, Cecchi E, Demichelis B, et al. Indicators of poor prognosis of acute pericarditis. *Circulation*. 2007;115:2739–2744.
387. Gouriet F, Levy PY, Casalta JP, et al. Etiology of pericarditis in a prospective cohort of 1162 cases. *Am J Med*. 2015;128:e1–e8.
388. Koontz CH, Ray CG. The role of Coxsackie group B virus infections in sporadic myopericarditis. *Am Heart J*. 1971;82:750–758.
389. Smith WG. Coxsackie B myopericarditis in adults. *Am Heart J*. 1970;80:34–46.
390. Grist NR, Bell EJ. Coxsackie viruses and the heart. *Am Heart J*. 1969;77:295–300.
391. Montgomery J, Gear J, Prinsloo FR, et al. Myocarditis of the newborn; an outbreak in a maternity home in Southern Rhodesia associated with Coxsackie group-B virus infection. *S Afr Med J*. 1955;29:608–612.
392. Bain HW, McLean DM, Walker SJ. Epidemic pleurodynia (Bornholm disease) due to Coxsackie B-5 virus. The inter-relationship of pleurodynia, benign pericarditis and aseptic meningitis. *Pediatrics*. 1961;27:889–903.
393. Van Reken D, Strauss A, Hernandez A, et al. Infectious pericarditis in children. *J Pediatr*. 1974;85:165–169.
394. Roberts R. Viral pericarditis. *Med Serv J Can*. 1961;17:588–596.
395. Movitt ER, Lenette EH, Mangum JF, et al. Acute benign pericarditis: report of 2 cases associated with group A and group B coxsackie viruses. *N Engl J Med*. 1958;158:1082–1086.
396. Matthews JD, Cameron SJ, George M. Constrictive pericarditis following Coxsackie virus infection. *Thorax*. 1970;25:624–626.
397. Boyle JD, Pearce ML, Guze LB. Purulent pericarditis: review of literature and report of eleven cases. *Medicine (Baltimore)*. 1961;40:119–144.
398. Rubin RH, Moellering RC. Clinical, microbiologic and therapeutic aspects of purulent pericarditis. *Am J Med*. 1975;59:68–78.
399. Kauffman CA, Watanakunakorn C, Phair JP. Purulent pneumococcal pericarditis. A continuing problem in the antibiotic era. *Am J Med*. 1973;54:743–750.
400. Saenz RE, Sanders CV, Aldridge KE, et al. Purulent pericarditis with associated cardiac tamponade caused by a *Streptococcus pneumoniae* strain highly resistant to penicillin, cefotaxime, and ceftriaxone. *Clin Infect Dis*. 1998;26:762–763.
401. Pruitt JL. Group A streptococcal pericarditis in a previously well child. *Pediatr Infect Dis J*. 1989;8:338.
402. Karim MA, Bach RG, Dressler F, et al. Purulent pericarditis caused by group B *Streptococcus* with pericardial tamponade. *Am Heart J*. 1993;126:727–730.
403. Kim NH, Park JP, Jeon SH, et al. Purulent pericarditis caused by group G *Streptococcus* as an initial presentation of colon cancer. *J Korean Med Sci*. 2002;17:571–573.
404. Kumar VV, Herzog C. Purulent pericarditis caused by group G *Streptococcus*. *JAMA*. 1990;264:34–35.
405. Hirata K, Asato H, Maeshiro M. A case of effusive constrictive pericarditis caused by *Streptococcus milleri*. *Jpn Circ J*. 1991;55:154–158.
406. Kopec JS, Grifka RG, Karpawich PP. Isolated staphylococcal pericarditis following varicella in an adolescent: an unusual age-associated complication. *Pediatr Emerg Care*. 1990;6:38–39.
407. Demey HE, Eycken M, Vandermast M, et al. Purulent pericarditis due to methicillin-resistant *Staphylococcus aureus*. A case report. *Acta Cardiol*. 1991;46:485–491.

408. Yoshioka H, Shigemitsu K, Takeuchi M, et al. *Salmonella* pericarditis in a patient with primary idiopathic chylopericardium. *Jpn J Thorac Cardiovasc Surg*. 2003;51:16–17.
409. Sanchez-Guerrero J, Alarcon-Segovia D. *Salmonella* pericarditis with tamponade in systemic lupus erythematosus. *Br J Rheumatol*. 1990;29:69–71.
410. Lecomte F, Eustache M, Lemeland JF, et al. Purulent pericarditis due to *Yersinia enterocolitica*. *J Infect Dis*. 1989;159:363.
411. Marshall BW, Zimmerman SL. Tularemic pericarditis. *AMA Arch Intern Med*. 1957;100:300–304.
412. Adams CW. Tularemic pericarditis; report of two cases and review of literature. *Dis Chest*. 1958;34:632–639.
413. El Hassan N, Dbaibo G, Diab K, et al. *Pseudomonas* pericarditis in an immunocompetent newborn: unusual presentation with review of the literature. *J Infect*. 2002;44:49–51.
414. Morrison VA, Lloyd BK, Chia JK, et al. Cardiovascular and bacteremic manifestations of *Campylobacter fetus* infection: case report and review. *Rev Infect Dis*. 1990;12:387–392.
415. Kanj SS, Araj GF, Taher A, et al. *Campylobacter fetus* pericarditis in a patient with beta-thalassemia: case report and review of the literature. *Clin Microbiol Infect*. 2001;7:510–513.
416. Ugartemendia MC, Curos-Abadal A, Pujol-Rakosnik M, et al. *Brucella melitensis* pericarditis. *Am Heart J*. 1985;109:1108.
417. Ramsdale DR, Gautam PC, Perera B, et al. Cardiac tamponade due to actinomycosis. *Thorax*. 1984;39:473–474.
418. O'Sullivan RA, Armstrong JG, Rivers JT, et al. Pulmonary actinomycosis complicated by effusive constrictive pericarditis. *Aust N Z J Med*. 1991;21:879–880.
419. Skiest DJ, Steiner D, Werner M, et al. Anaerobic pericarditis: case report and review. *Clin Infect Dis*. 1994;19:435–440.
420. Brook I. Pericarditis due to anaerobic bacteria. *Cardiology*. 2002;97:55–58.
421. Lam S, Greenberg R, Bank S. An unusual presentation of colon cancer: purulent pericarditis and cardiac tamponade due to *Bacteroides fragilis*. *Am J Gastroenterol*. 1995;90:1518–1520.
422. Touati GD, Carmi D, Nzomvuama A, et al. Purulent pericarditis caused by malignant oesophago-pericardial fistula. *Eur J Cardiothorac Surg*. 2003;24:847–849.
423. Blaser MJ, Reingold AL, Alsever RN, et al. Primary meningococcal pericarditis: a disease of adults associated with serogroup C *Neisseria meningitidis*. *Rev Infect Dis*. 1984;6:625–632.
424. Finkelstein Y, Adler Y, Nussinovitch M, et al. A new classification for pericarditis associated with meningococcal infection. *Eur J Pediatr*. 1997;156:585–588.
425. Morgan DR, Spence M, Crowe M, et al. Primary (isolated) meningococcal pericarditis. *Clin Cardiol*. 2002;25:305–307.
426. Coe MD, Hamer DH, Levy CS, et al. Gonococcal pericarditis with tamponade in a patient with systemic lupus erythematosus. *Arthritis Rheum*. 1990;33:1438–1441.
427. Wilson J, Zaman AG, Simmons AV. Gonococcal arthritis complicated by acute pericarditis and pericardial effusion. *Br Heart J*. 1990;63:134–135.
428. Farraj RS, McCully RB, Oh JK, et al. *Mycoplasma*-associated pericarditis. *Mayo Clin Proc*. 1997;72:33–36.
429. Sands MJ, Satz JE, Turner WE, et al. Pericarditis and perimyocarditis associated with active *Mycoplasma pneumoniae* infection. *Ann Intern Med*. 1977;86:544–548.
430. Mayock R, Skale B, Kohler RB. *Legionella pneumophila* pericarditis proved by culture of pericardial fluid. *Am J Med*. 1983;75:534–536.
431. Reyes RR, Noble RC. Legionnaires' pericarditis. *J Ky Med Assoc*. 1983;81:757–758.
432. Luck PC, Helbig JH, Wunderlich E, et al. Isolation of *Legionella pneumophila* serogroup 3 from pericardial fluid in a case of pericarditis. *Infection*. 1989;17:388–390.
433. Svendsen JH, Jonsson V, Niebuhr U. Combined pericarditis and pneumonia caused by *Legionella* infection. *Br Heart J*. 1987;58:663–664.
434. Puleo JA, Matar FA, McKeown PP, et al. *Legionella* pericarditis diagnosed by direct fluorescent antibody staining. *Ann Thorac Surg*. 1995;60:444–446.
435. Friedland L, Snydman DR, Weingarden AS, et al. Ocular and pericardial involvement in Legionnaires' disease. *Am J Med*. 1984;77:1105–1107.
436. Bruyn GA, De Koning J, Reijsoo FJ, et al. Lyme pericarditis leading to tamponade. *Br J Rheumatol*. 1994;33:862–866.
437. Dupuis C, Gronnier P, Kachaner J, et al. Bacterial pericarditis in infancy and childhood. *Am J Cardiol*. 1994;74:807–809.
438. Fyfe DA, Hagler DJ, Puga FJ, et al. Clinical and therapeutic aspects of *Haemophilus influenzae* pericarditis in pediatric patients. *Mayo Clin Proc*. 1984;59:415–422.
439. Schwartz KV, Guercio CA, Katz A. *Haemophilus influenzae* pericarditis. *Conn Med*. 1987;51:423–424.
440. Welikovitch L, Knight JL, Burggraf GW, et al. Cardiac tamponade secondary to *Haemophilus* pericarditis: a case report. *Can J Cardiol*. 1992;8:303–305.
441. Larrieu AJ, Tyers GF, Williams EH, et al. Recent experience with tuberculous pericarditis. *Ann Thorac Surg*. 1980;29:464–468.
442. Rooney JJ, Crocco JA, Lyons HA. Tuberculous pericarditis. *Ann Intern Med*. 1970;72:73–81.
443. Fowler NO. Tuberculous pericarditis. *JAMA*. 1991;266:99–103.
444. Sagrista-Sauleda J, Permanyer-Miralda G, Soler-Soler J. Tuberculous pericarditis: ten year experience with a prospective protocol for diagnosis and treatment. *J Am Coll Cardiol*. 1988;11:724–728.
445. Permanyer-Miralda G, Sagrista-Sauleda J, Soler-Soler J. Primary acute pericardial disease: a prospective series of 231 consecutive patients. *Am J Cardiol*. 1985;56:623–630.
446. Desai HN. Tuberculous pericarditis. A review of 100 cases. *S Afr Med J*. 1979;55:877–880.
447. Strang JI. Tuberculous pericarditis in Transkei. *Clin Cardiol*. 1984;7:667–670.
448. Strang JI, Kakaza HH, Gibson DG, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet*. 1988;2:759–764.
449. D'Cruz IA, Sengupta EE, Abrahams C, et al. Cardiac involvement, including tuberculous pericardial effusion, complicating acquired immune deficiency syndrome. *Am Heart J*. 1986;112:1100–1102.
450. Kwan T, Karve MM, Emerole O. Cardiac tamponade in patients infected with HIV. A report from an inner-city hospital. *Chest*. 1993;104:1059–1062.
451. Estok L, Wallach F. Cardiac tamponade in a patient with AIDS: a review of pericardial disease in patients with HIV infection. *Mt Sinai J Med*. 1998;65:33–39.
452. Ortbals DW, Avioli LV. Tuberculous pericarditis. *Arch Intern Med*. 1979;139:231–234.
453. Peel AA. Tuberculous pericarditis. *Br Heart J*. 1948;10:195–207.
454. Roberts WC, Spray TL. Clinical and morphologic spectrum of pericardial heart disease. *Curr Probl Cardiol*. 1977;2:1–71.
455. Strang JI, Kakaza HH, Gibson DG, et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet*. 1987;2:1418–1422.
456. Trautner BW, Darouiche RO. Tuberculous pericarditis: optimal diagnosis and management. *Clin Infect Dis*. 2001;33:954–961.
457. Wheat J. Histoplasmosis. Experience during outbreaks in Indianapolis and review of the literature. *Medicine (Baltimore)*. 1997;76:339–354.
458. Wheat LJ, Stein L, Corya BC, et al. Pericarditis as a manifestation of histoplasmosis during two large urban outbreaks. *Medicine (Baltimore)*. 1983;62:110–119.
459. McCarty JM, Demetral LC, Dabrowski L, et al. Pediatric coccidioidomycosis in central California: a retrospective case series. *Clin Infect Dis*. 2013;56:1579–1585.
460. Larson R, Scherb RE. Coccidioidal pericarditis. *Circulation*. 1953;7:211–217.
461. Chapman MG, Kaplan L. Cardiac involvement in coccidioidomycosis. *Am J Med*. 1957;23:87–98.
462. Schwartz EL, Waldmann EB, Payne RM, et al. Coccidioidal pericarditis. *Chest*. 1976;70:670–672.
463. Amundson DE. Perplexing pericarditis caused by coccidioidomycosis. *South Med J*. 1993;86:694–696.
464. Oudiz R, Mahaisavariya P, Peng SK, et al. Disseminated coccidioidomycosis with rapid progression to effusive-constrictive pericarditis. *J Am Soc Echocardiogr*. 1995;8:947–952.
465. Witorsch P, Utz JP. North American blastomycosis: a study of 40 patients. *Medicine (Baltimore)*. 1968;47:169–200.
466. Walsh TJ, Bulkley BH. *Aspergillus* pericarditis: clinical and pathologic features in the immunocompromised patient. *Cancer*. 1982;49:48–54.
467. Brusch JL. Cardiac infections in the immunosuppressed patient. *Infect Dis Clin North Am*. 2001;15:613–638.
468. Carrel TP, Schaffner A, Schmid ER, et al. Fatal fungal pericarditis after cardiac surgery and immunosuppression. *J Thorac Cardiovasc Surg*. 1991;101:161–164.
469. Canver CC, Patel AK, Kosolcharoen P, et al. Fungal purulent constrictive pericarditis in a heart transplant patient. *Ann Thorac Surg*. 1998;65:1792–1794.
470. Schrank JH, Dooley DP. Purulent pericarditis caused by *Candida* species: case report and review. *Clin Infect Dis*. 1995;21:182–187.
471. Kraus WE, Valenstein PN, Corey GR. Purulent pericarditis caused by *Candida*: report of three cases and identification of high-risk populations as an aid to early diagnosis. *Rev Infect Dis*. 1988;10:34–41.
472. Eng RH, Sen P, Browne K, et al. *Candida* pericarditis. *Am J Med*. 1981;70:867–869.
473. Kaufman LD, Seifert FC, Eilbott DJ, et al. *Candida* pericarditis and tamponade in a patient with systemic lupus erythematosus. *Arch Intern Med*. 1988;148:715–717.
474. Neughebauer B, Alvarez V, Harb T, et al. Constrictive pericarditis caused by *Candida glabrata* in an immunocompetent patient: case report and review of literature. *Scand J Infect Dis*. 2002;34:615–619.
475. Kaul S, Fishbein MC, Siegel RJ. Cardiac manifestations of acquired immune deficiency syndrome: a 1991 update. *Am Heart J*. 1991;122:535–544.
476. Lind A, Reinsch N, Neuhaus K, et al. Pericardial effusion of HIV-infected patients? Results of a prospective multicenter cohort study in the era of antiretroviral therapy. *Eur J Med Res*. 2011;16:480–483.
477. Woods GL, Goldsmith JC. Fatal pericarditis due to *Mycobacterium avium-intracellulare* in acquired immunodeficiency syndrome. *Chest*. 1989;95:1355–1357.
478. Moreno F, Sharkey-Mathis PK, Mokulis E, et al. *Mycobacterium kansasii* pericarditis in patients with AIDS. *Clin Infect Dis*. 1994;19:967–969.
479. Campo RE, Campo CE. *Mycobacterium kansasii* disease in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1997;24:1233–1238.
480. Pintado V, Fortun J, Casado JL, et al. *Mycobacterium kansasii* pericarditis as a presentation of AIDS. *Infection*. 2001;29:48–50.
481. Moreno R, Villacastin JP, Bueno H, et al. Clinical and echocardiographic findings in HIV patients with pericardial effusion. *Cardiology*. 1997;88:397–400.
482. LeWinter MM, Tischler MD. Pericardial diseases. In: Bonow RO, Mann DL, Zipes DP, et al, eds. *Braunwald's Heart Disease—A Textbook of Cardiovascular Medicine*. 9th ed. Philadelphia: Saunders; 2011:1651–1671.
483. Dalli E, Quesada A, Juan G, et al. Tuberculous pericarditis as the first manifestation of acquired immunodeficiency syndrome. *Am Heart J*. 1987;114:905–906.
484. Heidenreich PA, Eisenberg MJ, Kee LL, et al. Pericardial effusion in AIDS. Incidence and survival. *Circulation*. 1995;92:3229–3234.
485. Shabetai R, Abel DC, Graham JB, et al. Function of the pericardium and pericardioperitoneal canal in elasmobranch fishes. *Am J Physiol*. 1985;248:H198–H207.
486. Shabetai R. Acute pericarditis. *Cardiol Clin*. 1990;8:639–644.
487. Fowler NO. Recurrent pericarditis. *Cardiol Clin*. 1990;8:621–626.
488. Fowler NO, Harbin AD 3rd. Recurrent acute pericarditis: follow-up study of 31 patients. *J Am Coll Cardiol*. 1986;7:300–305.
489. Raatikka M, Pelkonen PM, Karjalainen J, et al. Recurrent pericarditis in children and adolescents: report of 15 cases. *J Am Coll Cardiol*. 2003;42:759–764.
490. Ribeiro P, Shapiro L, Nihoyannopoulos P, et al. Pericarditis in infective endocarditis. *Eur Heart J*. 1985;6:975–978.
491. Carson TJ, Murray GF, Wilcox BR, et al. The role of surgery in tuberculous pericarditis. *Ann Thorac Surg*. 1974;17:163–167.
492. Xu B, Harb SC, Cremer PC. New insights into pericarditis: mechanisms of injury and therapeutic targets. *Curr Cardiol Rep*. 2017;19:60.
493. Guberman BA, Fowler NO, Engel PJ, et al. Cardiac tamponade in medical patients. *Circulation*. 1981;64:633–640.
494. Troughton RW, Asher CR, Klein AL. Pericarditis. *Lancet*. 2004;363:717–727.
495. Spodick DH. Pericardial rub. Prospective, multiple observer investigation of pericardial friction in 100 patients. *Am J Cardiol*. 1975;35:357–362.
496. Talreja DR, Edwards WD, Danielson GK, et al. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. *Circulation*. 2003;108:1852–1857.
497. Spodick DH. Electrocardiogram in acute pericarditis. Distributions of morphologic and axial changes by stages. *Am J Cardiol*. 1974;33:470–474.
498. Spodick DH. Frequency of arrhythmias in acute pericarditis determined by Holter monitoring. *Am J Cardiol*. 1984;53:842–845.
499. Isner JM, Carter BL, Bankoff MS, et al. Computed tomography in the diagnosis of pericardial heart disease. *Ann Intern Med*. 1982;97:473–479.
500. Tomoda H, Hoshiai M, Furuya H, et al. Evaluation of pericardial effusion with computed tomography. *Am Heart J*. 1980;99:701–706.

501. Sechtem U, Tscholakoff D, Higgins CB. MRI of the abnormal pericardium. *AJR Am J Roentgenol*. 1986;147:245–252.
502. Giorgi B, Mollet NRA, Dymarkowski S, et al. Clinically suspected constrictive pericarditis: MR imaging assessment of ventricular septal motion and configuration in patients and healthy subjects. *Radiology*. 2003;228:417–424.
503. Rotbart HA, Eastman PS, Ruth JL, et al. Nonisotopic oligomeric probes for the human enteroviruses. *J Clin Microbiol*. 1988;26:2669–2671.
504. Krikorian JG, Hancock EW. Pericardiocentesis. *Am J Med*. 1978;65:808–814.
505. Corey GR, Campbell PT, Van Trigt P, et al. Etiology of large pericardial effusions. *Am J Med*. 1993;95:209–213.
506. Gouny P, Lancelin C, Girard PM, et al. Pericardial effusion and AIDS: benefits of surgical drainage. *Eur J Cardiothorac Surg*. 1998;13:165–169.
507. Uthaman B, Endrys J, Abushaban L, et al. Percutaneous pericardial biopsy: technique, efficacy, safety, and value in the management of pericardial effusion in children and adolescents. *Pediatr Cardiol*. 1997;18:414–418.
508. Selig MB. Percutaneous pericardial biopsy under echocardiographic guidance. *Am Heart J*. 1991;122:879–882.
509. Schifferdecker B, Spodick DH. Nonsteroidal anti-inflammatory drugs in the treatment of pericarditis. *Cardiol Rev*. 2003;11:211–217.
510. Imazio M, Demichelis B, Parrini I, et al. Day-hospital treatment of acute pericarditis: a management program for outpatient therapy. *J Am Coll Cardiol*. 2004;43:1042–1046.
511. Imazio M, Brucato A, Cemin R, et al. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369:1522–1528.
512. Alabed S, Cabello JB, Irving GJ, et al. Colchicine for pericarditis. *Cochrane Database Syst Rev*. 2014;(8):CD010652.
513. Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation*. 2005;112:2012–2016.
514. Quale JM, Lipschik GY, Heurich AE. Management of tuberculous pericarditis. *Ann Thorac Surg*. 1987;43:653–655.
515. Marcolongo R, Russo R, Laveder F, et al. Immunosuppressive therapy prevents recurrent pericarditis. *J Am Coll Cardiol*. 1995;26:1276–1279.
516. Tan JS, Holmes JC, Fowler NO, et al. Antibiotic levels in pericardial fluid. *J Clin Invest*. 1974;53:7–12.
517. Utley JR, Mills J. Annular erosion and pericarditis. Complications of endocarditis of the aortic root. *J Thorac Cardiovasc Surg*. 1972;64:76–81.
518. Augustin P, Desmard M, Mordant P, et al. Clinical review: intrapericardial fibrinolysis in management of purulent pericarditis. *Crit Care*. 2011;15:220.
519. Suwan PK. Potjalongsilp S. Predictors of constrictive pericarditis after tuberculous pericarditis. *Br Heart J*. 1995;73:187–189.
520. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clin Infect Dis*. 1997;25:872–887.
521. Alzeer AH, Fitzgerald JM. Corticosteroids and tuberculosis: risks and use as adjunct therapy. *Tuber Lung Dis*. 1993;74:6–11.
522. Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*. 2014;371:1121–1130.
523. Fennell WM. Surgical treatment of constrictive tuberculous pericarditis. *S Afr Med J*. 1982;62: 353–355.
524. Arsan S, Mercan S, Sarigul A, et al. Long-term experience with pericardiectomy: analysis of 105 consecutive patients. *Thorac Cardiovasc Surg*. 1994;42:340–344.
525. Bozbuga N, Erentug V, Eren E, et al. Pericardiectomy for chronic constrictive tuberculous pericarditis: risks and predictors of survival. *Tex Heart Inst J*. 2003;30:180–185.
526. Ustunsoy H, Celkan MA, Sivrikoz MC, et al. Intrapericardial fibrinolytic therapy in purulent pericarditis. *Eur J Cardiothorac Surg*. 2002;22:373–376.
527. Mahfoud F, Gartner B, Kindermann M, et al. Virus serology in patients with suspected myocarditis: utility or futility? *Eur Heart J*. 2011;32:897–903.
528. Karjalainen J, Heikkila J, Nieminen MS, et al. Etiology of mild acute infectious myocarditis. Relation to clinical features. *Acta Med Scand*. 1983;213:65–73.
529. Morita H, Kitaura Y, Deguchi H, et al. Coxsackie B5 myopericarditis in a young adult—clinical course and endomyocardial biopsy findings. *Jpn Circ J*. 1983;47:1077–1083.
530. Bowles NE, Ni J, Marcus F, et al. The detection of cardiotropic viruses in the myocardium of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2002;39:892–895.
531. Chany C, Lepine P, Lelong M, et al. Severe and fatal pneumonia in infants and young children associated with adenovirus infections. *Am J Hyg*. 1958;67:367–378.
532. Berkovich S, Rodriguez-Torres R, Lin JS. Virologic studies in children with acute myocarditis. *Am J Dis Child*. 1968;115:207–212.
533. Odio C, McCracken GH, Nelson JD. Disseminated adenovirus infection: a case report and review of the literature. *Pediatr Infect Dis*. 1984;3:46–49.
534. Russell SJ, Bell EJ. Echoviruses and carditis. *Lancet*. 1970;1:784–785.
535. Bell EJ, Grist NR. ECHO viruses, carditis, and acute pleurodynia. *Am Heart J*. 1971;82:133–135.
536. Fukuhara T, Kinoshita M, Bito K, et al. Myopericarditis associated with ECHO virus type 3 infection—a case report. *Jpn Circ J*. 1983;47:1274–1280.
537. Celers J, Celers P, Bertocchi A. [Non-polio enterovirus in France from 1974 to 1985. Data collected from a system of 30 hospital virology laboratories]. *Pathol Biol (Paris)*. 1988;36:1221–1226.
538. Grist NR, Bell EJ, Assaad F. Enteroviruses in human disease. *Prog Med Virol*. 1978;24:114–157.
539. Enders G, Dotsch J, Bauer J, et al. Life-threatening parvovirus B19-associated myocarditis and cardiac transplantation as possible therapy: two case reports. *Clin Infect Dis*. 1998;26:355–358.
540. Schowengerdt KO, Ni J, Denfield SW, et al. Association of parvovirus B19 genome in children with myocarditis and cardiac allograft rejection: diagnosis using the polymerase chain reaction. *Circulation*. 1997;96:3549–3554.
541. Munro K, Croxson MC, Thomas S, et al. Three cases of myocarditis in childhood associated with human parvovirus (B19 virus). *Pediatr Cardiol*. 2003;24:473–475.
542. Bultmann BD, Klingel K, Sotlar K, et al. Parvovirus B19: a pathogen responsible for more than hematologic disorders. *Virchows Arch*. 2003;442:8–17.
543. Lamparter S, Schoppet M, Pankuweit S, et al. Acute parvovirus B19 infection associated with myocarditis in an immunocompetent adult. *Hum Pathol*. 2003;34:725–728.
544. Jungeblut CW, Edwards JE. Isolation of poliomyelitis virus from the heart in fatal cases. *Am J Clin Pathol*. 1951;21:601–623.
545. Weinstein L, Shelokov A. Cardiovascular manifestations in acute poliomyelitis. *N Engl J Med*. 1951;244:281–285.
546. Ross E, Armentrout SA. Myocarditis associated with rabies. Report of a case. *N Engl J Med*. 1962;266:1087–1089.
547. Cheetham HD, Hart J, Coghill NF, et al. Rabies with myocarditis. Two cases in England. *Lancet*. 1970;1:921–922.
548. Raman GV, Prosser A, Spreadbury PL, et al. Rabies presenting with myocarditis and encephalitis. *J Infect*. 1988;17:155–158.
549. Roberts WC, Fox SM. Mumps of the heart. Clinical and pathologic features. *Circulation*. 1965;32:342–345.
550. Chaudary S, Jaski BE. Fulminant mumps myocarditis. *Ann Intern Med*. 1989;110:569–570.
551. Kabakus N, Aydinoglu H, Yekeler H, et al. Fatal mumps nephritis and myocarditis. *J Trop Pediatr*. 1999;45:358–360.
552. Hamburger WW. The heart in influenza. *Med Clin North Am*. 1938;22:111–121.
553. Verel D, Warrack AJ, Potter CW, et al. Observations on the A2 England influenza epidemic: a clinicopathological study. *Am Heart J*. 1976;92:290–296.
554. Proby CM, Hackett D, Gupta S, et al. Acute myopericarditis in influenza A infection. *Q J Med*. 1986;60:887–892.
555. Adams CW. Postviral myopericarditis associated with the influenza virus; report of eight cases. *Am J Cardiol*. 1959;4:56–67.
556. Ainger LE, Lawyer NG, Fitch CW. Neonatal rubella myocarditis. *Br Heart J*. 1966;28:691–697.
557. Kriseman T. Rubella myocarditis in a 9-year-old patient. *Clin Pediatr (Phila)*. 1984;23:240–241.
558. Chuah SK. Transient ventricular arrhythmia as a cardiac manifestation in dengue haemorrhagic fever—a case report. *Singapore Med J*. 1987;28:569–572.
559. Obeyesekere I, Hermon Y. Myocarditis and cardiomyopathy after arbovirus infections (dengue and chikungunya fever). *Br Heart J*. 1972;34:821–827.
560. Cannell DE. Myocardial degenerations in yellow fever. *Am J Pathol*. 1928;4:431–443.
561. Milei J, Bolomo NJ. Myocardial damage in viral hemorrhagic fevers. *Am Heart J*. 1982;104:1385–1391.
562. Thiede WH. Cardiac involvement in lymphocytic choriomeningitis. *Arch Intern Med*. 1962;109:50–54.
563. Cummins D, Bennett D, Fisher-Hoch SP, et al. Lassa fever encephalopathy: clinical and laboratory findings. *J Trop Med Hyg*. 1992;95:197–201.
564. Cummins D, Bennett D, Fisher-Hoch SP, et al. Electrocardiographic abnormalities in patients with Lassa fever. *J Trop Med Hyg*. 1989;92:350–355.
565. Yanase O, Motomiya T, Watanabe K, et al. [Lassa fever associated with effusive constrictive pericarditis and bilateral atrioventricular annular constriction: a case report]. *J Cardiol*. 1989;19:1147–1156.
566. Waagner DC, Murphy TV. Varicella myocarditis. *Pediatr Infect Dis J*. 1990;9:360–363.
567. Alter P, Grimm W, Maisch B. [Reversible grade III atrioventricular block in a 35-year-old patient]. *Internist (Berl)*. 2001;42:901–904.
568. Woolf PK, Chung TS, Stewart J, et al. Life-threatening dysrhythmias in varicella myocarditis. *Clin Pediatr (Phila)*. 1987;26:480–482.
569. Coppack SW, Doshi R, Ghose AR. Fatal varicella in a healthy young adult. *Postgrad Med J*. 1985;61:529–531.
570. Tsintsof A, Delprado WJ, Keogh AM. Varicella zoster myocarditis progressing to cardiomyopathy and cardiac transplantation. *Br Heart J*. 1993;70:93–95.
571. Fiddler GI, Campbell RW, Pottage A, et al. Varicella myocarditis presenting with unusual ventricular arrhythmias. *Br Heart J*. 1977;39:1150–1153.
572. Noren GR, Tobin JD, Staley NA, et al. Association of varicella, myocarditis, and congestive cardiomyopathy. *Pediatr Cardiol*. 1982;3:53–57.
573. Lorber A, Zonis Z, Maisuls E, et al. The scale of myocardial involvement in varicella myocarditis. *Int J Cardiol*. 1988;20:257–262.
574. Kundu AK. Herpes zoster-induced myocarditis in a patient with diabetes mellitus. *J Assoc Physicians India*. 2001;49:286–287.
575. Tiula E, Leinikki P. Fatal cytomegalovirus infection in a previously healthy boy with myocarditis and consumption coagulopathy as presenting signs. *Scand J Infect Dis*. 1972;4:57–60.
576. Maisch B, Schonian U, Crombach M, et al. Cytomegalovirus associated inflammatory heart muscle disease. *Scand J Infect Dis Suppl*. 1993;88:135–148.
577. Millett R, Tomita T, Marshall HE, et al. Cytomegalovirus endomyocarditis in a transplanted heart. A case report with in situ hybridization. *Arch Pathol Lab Med*. 1991;115:511–515.
578. Ando H, Shiramizu T, Hisanou R. Dilated cardiomyopathy caused by cytomegalovirus infection in a renal transplant recipient. *Jpn Heart J*. 1992;33:409–412.
579. Arbustini E, Grasso M, Diegoli M, et al. Histopathologic and molecular profile of human cytomegalovirus infections in patients with heart transplants. *Am J Clin Pathol*. 1992;98:205–213.
580. Powell KF, Bellamy AR, Catton MG, et al. Cytomegalovirus myocarditis in a heart transplant recipient: sensitive monitoring of viral DNA by the polymerase chain reaction. *J Heart Transplant*. 1989;8:465–470.
581. Webster BH. Cardiac complications of infectious mononucleosis; a review of the literature and report of five cases. *Am J Med Sci*. 1957;234:62–70.
582. Fraisse A, Paut O, Zandotti C, et al. [Epstein-Barr virus. An unusual cause of acute myocarditis in children]. *Arch Pediatr*. 2000;7:752–755.
583. Tyson AA, Hackshaw BT, Kutcher MA. Acute Epstein-Barr virus myocarditis simulating myocardial infarction with cardiogenic shock. *South Med J*. 1989;82:1184–1187.
584. Hebert MM, Yu C, Towbin JA, et al. Fatal Epstein-Barr virus myocarditis in a child with repetitive myocarditis. *Pediatr Pathol Lab Med*. 1995;15:805–812.
585. Baykurt C, Caglar K, Ceviz N, et al. Successful treatment of Epstein-Barr virus infection associated with myocarditis. *Pediatr Int*. 1999;41:389–391.
586. Frishman W, Kraus ME, Zabkar J, et al. Infectious mononucleosis and fatal myocarditis. *Chest*. 1977;72:535–538.
587. Cheng TC. Severe chest pain due to infectious mononucleosis. *Postgrad Med*. 1983;73:149–150, 153–154.
588. Sabbatani S, Manfredi R, Ortolani P, et al. Myopericarditis during a primary Epstein-Barr virus infection in an otherwise healthy young adult. An unusual and insidious complication. Case report and a 60-year literature review. *Infez Med*. 2012;20:75–81.
589. Andreoletti L, Leveque N, Boulagnon C, et al. Viral causes of human myocarditis. *Arch Cardiovasc Dis*. 2009;102:559–568.
590. Leveque N, Boulagnon C, Brasselet C, et al. A fatal case of human herpesvirus 6 chronic myocarditis in an immunocompetent adult. *J Clin Virol*. 2011;52:142–145.
591. Whorton CM, Thomas DM, Denham SW. Fatal systemic herpes simplex virus type 2 infection in a healthy young woman. *South Med J*. 1983;76:81–83.
592. Young EJ, Chafizadeh E, Oliveira VL, et al. Disseminated herpesvirus infection during pregnancy. *Clin Infect Dis*. 1996;22:51–58.

593. Anderson T, Foulis MA, Grist NR, et al. Clinical and laboratory observations in a small pox outbreak. *Lancet*. 1951;1:1248–1252.
594. Macadam DB, Whitaker W. Cardiac complication after vaccination for smallpox. *BMJ*. 1962;5312:1099–1100.
595. Matthews AW, Griffiths ID. Post-vaccinial pericarditis and myocarditis. *Br Heart J*. 1974;36:1043–1045.
596. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. *JAMA*. 2003;289:3283–3289.
597. Saurina G, Shirazi S, Lane JM, et al. Myocarditis after smallpox vaccination: a case report. *Clin Infect Dis*. 2003;37:145–146.
598. Cono J, Casey CG, Bell DM. Smallpox vaccination and adverse reactions. Guidance for clinicians. *MMWR Recomm Rep*. 2003;52:1–28.
599. Mahapatra RK, Ellis GH. Myocarditis and hepatitis B virus. *Angiology*. 1985;36:116–119.
600. Bell H. Cardiac manifestations of viral hepatitis. *JAMA*. 1971;218:387–391.
601. Ursell PC, Habib A, Sharma P, et al. Hepatitis B virus and myocarditis. *Hum Pathol*. 1984;15:481–484.
602. Matsumori A, Yutani C, Ikeda Y, et al. Hepatitis C virus from the hearts of patients with myocarditis and cardiomyopathy. *Lab Invest*. 2000;80:1137–1142.
603. Okabe M, Fukuda K, Arakawa K, et al. Chronic variant of myocarditis associated with hepatitis C virus infection. *Circulation*. 1997;96:22–24.
604. Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. *Circulation*. 1995;92:2519–2525.
605. Thomas JA, Raroque S, Scott WA, et al. Successful treatment of severe dysrhythmias in infants with respiratory syncytial virus infections: two cases and a literature review. *Crit Care Med*. 1997;25:880–886.
606. Checchia PA, Appel HJ, Kahn S, et al. Myocardial injury in children with respiratory syncytial virus infection. *Pediatr Crit Care Med*. 2000;1:146–150.
607. Barbaro G, Di Lorenzo G, Grisorio B, et al. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV-positive patients. Gruppo Italiano per lo Studio Cardiologico dei Pazienti Affetti da AIDS. *N Engl J Med*. 1998;339:1093–1099.
608. Rubenstein JS, Noah ZL, Zales VR, et al. Acute myocarditis associated with *Shigella sonnei* gastroenteritis. *J Pediatr*. 1993;122:82–84.
609. Leon F, Badui E, Campos A, et al. Cholera and myocarditis—a case report. *Angiology*. 1997;48:545–549.
610. Dada MA, Lazarus NG, Kharsany AB, et al. Sudden death caused by myocardial tuberculosis: case report and review of the literature. *Am J Forensic Med Pathol*. 2000;21:385–388.
611. Diaz-Peromingo JA, Marino-Callejo AI, Gonzalez-Gonzalez C, et al. Tuberculous myocarditis presenting as long QT syndrome. *Eur J Intern Med*. 2000;11:340–342.
612. Fournier PE, Etienne J, Harle JR, et al. Myocarditis, a rare but severe manifestation of Q fever: report of 8 cases and review of the literature. *Clin Infect Dis*. 2001;32:1440–1447.
613. Million M, Walter G, Thuny F, et al. Evolution from acute q fever to endocarditis is associated with underlying valvulopathy and age and can be prevented by prolonged antibiotic treatment. *Clin Infect Dis*. 2013;57:836–844.
614. Williams JD, Snow RM, Arciniegas JG. Myocardial involvement in a patient with human ehrlichiosis. *Am J Med*. 1995;98:414–415.
615. Havens NS, Kinnear BR, Mato S. Fatal ehrlichial myocarditis in a healthy adolescent: a case report and review of the literature. *Clin Infect Dis*. 2012;54:e113–e114.
616. Silvestry FE, Kim B, Pollack BJ, et al. Cardiac Whipple disease: identification of Whipple bacillus by electron microscopy of a patient before death. *Ann Intern Med*. 1997;126:214–216.
617. Tarrant WP, Gonzalez-Berjon JM, Cernoch PL, et al. Spontaneous bacterial pericarditis with tamponade due to *Ureaplasma* spp. *J Clin Microbiol*. 2009;47:1965–1968.
618. Hidron A, Vogenthaler N, Santos-Preciado JI, et al. Cardiac involvement with parasitic infections. *Clin Microbiol Rev*. 2010;23:324–349.
619. de Carvalho VB, Sousa EF, Vila JH, et al. Heart transplantation in Chagas' disease. 10 years after the initial experience. *Circulation*. 1996;94:1815–1817.
620. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas' disease in the United States: a systematic review. *JAMA*. 2007;298:2171–2181.
621. Dao AH, Virmani R. Visceral larva migrans involving the myocardium: report of two cases and review of literature. *Pediatr Pathol*. 1986;6:449–456.
622. Abe K, Shimokawa H, Kubota T, et al. Myocarditis associated with visceral larva migrans due to *Toxocara canis*. *Intern Med*. 2002;41:706–708.
623. Fowler NO. The secondary cardiomyopathies. In: Fowler NO, ed. *Myocardial Disease*. New York: Grune & Stratton; 1973:337–359.
624. Ansari A, Larson PH, Bates HD. Cardiovascular manifestations of systemic lupus erythematosus: current perspective. *Prog Cardiovasc Dis*. 1985;27:421–434.
625. Clemson BS, Miller WR, Luck JC, et al. Acute myocarditis in fulminant systemic sclerosis. *Chest*. 1992;101:872–874.
626. McWhorter JE 4th, LeRoy EC. Pericardial disease in scleroderma (systemic sclerosis). *Am J Med*. 1974;57:566–575.
627. Janosik DL, Osborn TG, Moore TL, et al. Heart disease in systemic sclerosis. *Semin Arthritis Rheum*. 1989;19:191–200.
628. Lebowitz WB. The heart in rheumatoid arthritis (rheumatoid disease). A clinical and pathological study of sixty-two cases. *Ann Intern Med*. 1963;58:102–123.
629. Goldenberg J, Ferraz MB, Pessoa AP, et al. Symptomatic cardiac involvement in juvenile rheumatoid arthritis. *Int J Cardiol*. 1992;34:57–62.
630. Askari AD, Huettner TL. Cardiac abnormalities in polymyositis/dermatomyositis. *Semin Arthritis Rheum*. 1982;12:208–219.
631. Tami LF, Bhasin S. Polymorphism of the cardiac manifestations in dermatomyositis. *Clin Cardiol*. 1993;16:260–264.
632. Bank I, Marboe CC, Redberg RF, et al. Myocarditis in adult Still's disease. *Arthritis Rheum*. 1985;28:452–454.
633. Webb JG, Butany J, Langer G, et al. Myocarditis and myocardial hemorrhage associated with thrombotic thrombocytopenic purpura. *Arch Intern Med*. 1990;150:1535–1537.
634. Midei MG, DeMent SH, Feldman AM, et al. Peripartum myocarditis and cardiomyopathy. *Circulation*. 1990;81:922–928.
635. Ikaheimo MJ, Niemela KO, Linnaluoto MM, et al. Early cardiac changes related to radiation therapy. *Am J Cardiol*. 1985;56:943–946.
636. Brosius FC, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med*. 1981;70:519–530.
637. Stewart JR, Fajardo LF. Radiation-induced heart disease: an update. *Prog Cardiovasc Dis*. 1984;27:173–194.
638. Isner JM, Chokshi SK. Cardiac complications of cocaine abuse. *Annu Rev Med*. 1991;42:133–138.
639. Taliercio CP, Olney BA, Lie JT. Myocarditis related to drug hypersensitivity. *Mayo Clin Proc*. 1985;60:463–468.
640. Brand A, Keren A, Kerem E, et al. Myocardial damage after a scorpion sting: long-term echocardiographic follow-up. *Pediatr Cardiol*. 1988;9:59–61.
641. Matsuura H, Ishikita T, Yamamoto S, et al. Gallium-67 myocardial imaging for the detection of myocarditis in the acute phase of Kawasaki disease (mucocutaneous lymph node syndrome): the usefulness of single photon emission computed tomography. *Br Heart J*. 1987;58:385–392.
642. Humbert P, Faivre R, Fellman D, et al. Giant cell myocarditis: an autoimmune disease? *Am Heart J*. 1988;115:485–487.
643. Temple-Camp CR. Sarcoid myocarditis: a report of three cases. *N Z Med J*. 1989;102:501–502.
644. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation*. 1978;58:1204–1211.
645. Kleinfeld M, Milles S, Lidsky M. Mumps pericarditis: review of the literature and report of a case. *Am Heart J*. 1958;55:153–156.
646. Hildebrandt HM, Maassab HF, Willis PW 3rd. Influenza virus pericarditis. Report of a case with isolation of Asian influenza virus from the pericardial fluid. *Am J Dis Child*. 1962;104:579–582.
647. Williams AJ, Freemont AJ, Barnett DB. Pericarditis and arthritis complicating chickenpox. *Br J Clin Pract*. 1983;37:226–227.
648. Kassab A, Demoulin JC, Vanlancker MA, et al. Cytomegalovirus hemopericarditis. Report of 1 case with histologic confirmation. *Acta Cardiol*. 1987;42:69–72.
649. Martin V, Miranda ML, Stiefel P, et al. [Acute pericarditis caused by cytomegalovirus in a normal host]. *Enferm Infecc Microbiol Clin*. 1989;7:515.
650. Nathan PE, Arsura EL, Zappi M. Pericarditis with tamponade due to cytomegalovirus in the acquired immunodeficiency syndrome. *Chest*. 1991;99:765–766.
651. Scott PJ, Conway SP, Da Costa P. Cardiac tamponade complicating cytomegalovirus pericarditis in a patient with AIDS. *J Infect*. 1990;20:92–93.
652. Campbell PT, Li JS, Wall TC, et al. Cytomegalovirus pericarditis: a case series and review of the literature. *Am J Med Sci*. 1995;309:229–234.
653. Freedberg RS, Gindea AJ, Dieterich DT, et al. Herpes simplex pericarditis in AIDS. *N Y State J Med*. 1987;87:304–306.
654. Toma E, Poisson M, Claessens MR, et al. Herpes simplex type 2 pericarditis and bilateral facial palsy in a patient with AIDS. *J Infect Dis*. 1989;160:553–554.
655. Yoshida M, Nakamae H, Okamura H, et al. Pericarditis associated with human herpesvirus-6 reactivation in a patient after unrelated cord blood transplant. *Exp Clin Transplant*. 2017;15:235–238.
656. Centers for Disease Control and Prevention. Update: cardiac-related events during the civilian smallpox vaccination program—United States, 2003. *JAMA*. 2003;290:31–34.
657. Bateman AC, Richards M, Pallett AP. Fatal myocarditis associated with a Lancefield group B *Streptococcus*. *J Infect*. 1998;36:354–355.
658. Tokuyasu H, Saitoh Y, Harada T, et al. Purulent pericarditis caused by the *Streptococcus milleri* group: a case report and review of the literature. *Intern Med*. 2009;48:1073–1078.
659. Evans ME, Gregory DW, Schaffner W, et al. Tularemia: a 30-year experience with 88 cases. *Medicine (Baltimore)*. 1985;64:251–269.
660. Ferguson R, Yee S, Finkle H, et al. *Listeria*-associated pericarditis in an AIDS patient. *J Natl Med Assoc*. 1993;85:225–228.
661. Poland GA, Jorgensen CR, Sarosi GA. *Nocardia asteroides* pericarditis: report of a case and review of the literature. *Mayo Clin Proc*. 1990;65:819–824.
662. Krassas A, Sakellaridis T, Argyriou M, et al. Pyopericardium followed by constrictive pericarditis due to *Corynebacterium diphtheriae*. *Interact Cardiovasc Thorac Surg*. 2012;14:875–877.
663. Blaas SH, Böhm S, Martin G, et al. Pericarditis as primary manifestation of *Mycobacterium bovis* subsp. *caprae* infection. *Diagnost Microbiol Infect Dis*. 2003;47:431–433.
664. Balaguer A, Boronat M, Carrascosa A. Successful treatment of pericarditis associated with *Mycoplasma pneumoniae* infection. *Pediatr Infect Dis J*. 1990;9:141–143.
665. Kenney RT, Li JS, Clyde WA Jr, et al. Mycoplasmal pericarditis: evidence of invasive disease. *Clin Infect Dis*. 1993;17(suppl 1):S58–S62.
666. Valero F, de Groote P, Millaire A, et al. Pericardial effusion as the initial feature of Q fever. *Am Heart J*. 1995;130:1308–1309.
667. Cooper JA, Weinbaum DL, Aldrich TK, et al. Invasive aspergillosis of the lung and pericardium in a nonimmunocompromised 33 year old man. *Am J Med*. 1981;71:903–907.
668. Ross EM, Macher AM, Roberts WC. *Aspergillus fumigatus* thrombi causing total occlusion of both coronary arterial ostia, all four major epicardial coronary arteries and coronary sinus and associated with purulent pericarditis. *Am J Cardiol*. 1985;56:499–500.
669. Le Moing V, Lortholary O, Timsit JF, et al. *Aspergillus* pericarditis with tamponade: report of a successfully treated case and review. *Clin Infect Dis*. 1998;26:451–460.
670. Rab SM, Alam N, Hoda AN, et al. Amoebic liver abscess. Some unique presentations. *Am J Med*. 1967;43: 811–816.
671. Baid CS, Varma AR, Lakhotia M. A case of subacute effusive constrictive pericarditis with a probable amoebic aetiology. *Br Heart J*. 1987;58:296–298.
672. Strang JI. Two-dimensional echocardiography in the diagnosis of amoebic pericarditis. A case report. *S Afr Med J*. 1987;71:328–329.
673. Sagrista-Sauleda J, Permanyer-Miralda G, Juste-Sanchez C, et al. Huge chronic pericardial effusion caused by *Toxoplasma gondii*. *Circulation*. 1982;66:895–897.
674. Lyngberg KK, Vennervald BJ, Bygbjerg IC, et al. *Toxoplasma* pericarditis mimicking systemic lupus erythematosus. Diagnostic and treatment difficulties in one patient. *Ann Med*. 1992;24:337–340.
675. Herry I, Philippe B, Hennequin C, et al. Acute life-threatening toxocaral tamponade. *Chest*. 1997;112:1692–1693.
676. van der Horst R. Schistosomiasis of the pericardium. *Trans R S Trop Med Hyg*. 1979;73:243–244.
677. Galve E, Garcia-Del-Castillo H, Evangelista A, et al. Pericardial effusion in the course of myocardial infarction: incidence, natural history, and clinical relevance. *Circulation*. 1986;73:294–299.
678. Gregoratos G. Pericardial involvement in acute myocardial infarction. *Cardiol Clin*. 1990;8:601–608.
679. Krainin FM, Flessas AP, Spodick DH. Infarction-associated pericarditis. Rarity of diagnostic electrocardiogram. *N Engl J Med*. 1984;311:1211–1214.
680. Khan AH. The postcardiac injury syndromes. *Clin Cardiol*. 1992;15:67–72.

681. Imazio M, Negro A, Belli R, et al. Frequency and prognostic significance of pericarditis following acute myocardial infarction treated by primary percutaneous coronary intervention. *Am J Cardiol.* 2009;103:1525–1529.
682. Imazio M, Hoit BD. Post-cardiac injury syndromes. An emerging cause of pericardial diseases. *Int J Cardiol.* 2013;168:648–652.
683. Renfrew R, Buselmeier TJ, Kjellstrand CM. Pericarditis and renal failure. *Annu Rev Med.* 1980;31:345–360.
684. Rutsky EA, Rostand SG. Treatment of uremic pericarditis and pericardial effusion. *Am J Kidney Dis.* 1987;10:2–8.
685. Wacker W, Merrill JP. Uremic pericarditis in acute and chronic renal failure. *J Am Med Assoc.* 1954;156:764–765.
686. Khan I, McCreery C. Images in clinical medicine. Uremic pericarditis. *N Engl J Med.* 2013;369:e17.
687. Saner HE, Gobel FL, Nicoloff DM, et al. Aortic dissection presenting as pericarditis. *Chest.* 1987;91:71–74.
688. Kelly CA, Bourke JP, Malcolm A, et al. Chronic pericardial disease in patients with rheumatoid arthritis: a longitudinal study. *Q J Med.* 1990;75:461–470.
689. Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. *Curr Opin Rheumatol.* 2011;23:57.
690. Abid MA, Gitlin N. Pericarditis—an extraintestinal complication of inflammatory bowel disease. *West J Med.* 1990;153:314–315.
691. Zimmerman J, Yahalom J, Bar-On H. Clinical spectrum of pericardial effusion as the presenting feature of hypothyroidism. *Am Heart J.* 1983;106:770–771.

85 Mediastinitis

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SHORT VIEW SUMMARY

Definition
- Mediastinitis is an infection involving the structures of the mediastinum (see Fig. 85.1).

Epidemiology
- Acute mediastinitis usually occurs via one of three routes: esophageal perforation, extension of a head and neck infection (descending necrotizing mediastinitis), and post–cardiac surgery (see Table 85.1).
- Post–cardiac surgery mediastinitis occurs in 1% to 2% of cardiac surgery cases, and important risk factors for mediastinitis include obesity, diabetes, *Staphylococcus aureus* colonization, use of bilateral internal thoracic arteries for coronary artery bypass, need for reexploration, and receipt of multiple blood products.
- Chronic/fibrosing mediastinitis is not technically an infection but is due to an excessive immune reaction to *Histoplasma* antigens in mediastinal lymph nodes, which results in fibrosis and narrowing of mediastinal structures.

Microbiology
- Oral microbiota, including streptococci, gram-negative bacilli, and anaerobes, predominate in mediastinitis due to esophageal perforation and descending head and neck infections.
- Poststernotomy mediastinitis is most frequently due to gram-positive cocci, especially staphylococci, whereas gram-negative bacilli and *Candida* are less common.

Diagnosis
- Esophageal rupture is usually manifested by chest pain, shortness of breath, and odynophagia.
- Signs of the initiating head and neck infection (swelling, pain, erythema) predominate in descending necrotizing mediastinitis.
- Post–cardiac surgery mediastinitis findings may range from subtle to fulminant but usually present within 2 weeks of surgery. Fever, wound drainage, cellulitis, and chest pain are often present.
- Laboratory findings may include leukocytosis and a rising procalcitonin in postmedian sternotomy patients.
- Fibrosing mediastinitis manifestations include cough, dyspnea, chest pain, and exercise intolerance but depend on the structures occluded.
- Computed tomography is the preferred diagnostic imaging for all forms of mediastinitis.

Therapy
- Broad-spectrum antimicrobials targeted to expected pathogens are essential.
- Aggressive surgical intervention is essential in all forms of infectious mediastinitis, with débridement of any infected or necrotic tissues.
- Esophageal perforation, if recognized early, is increasingly managed with stenting and broad-spectrum antibiotics, but many cases still require surgical repair.
- Post–cardiac surgery mediastinitis requires sternal and mediastinal débridement.
- Multiple surgical techniques for surgical treatment of poststernotomy mediastinitis can be used, with increasing use of negative pressure wound therapy and soft tissue flaps for reconstruction.
- The role, if any, for antifungal therapy in fibrosing mediastinitis is not established.
- In fibrosing mediastinitis, stenoses of vessels and other structures can be managed by surgical bypass or stenting.

Prevention
- Prevention of post–cardiac surgery is a major focus of quality measures and guidelines.
- Key factors associated with decreased post–cardiac surgery infection rates include appropriate antimicrobial prophylaxis (administration of an appropriate agent within 1 hour before surgery and for no longer than 24–48 hours), control of postoperative blood glucose, and perioperative use of nasal mupirocin in patients known to be colonized with *S. aureus*.

Mediastinitis can be organized into acute or chronic forms with etiologies, clinical presentations, and treatments that are strikingly different. Acute mediastinitis is an uncommon but potentially devastating infection involving the structures of the mediastinum. Before the development of sophisticated techniques in cardiovascular and thoracic surgery, most cases resulted from esophageal perforation or contiguous spread from oropharyngeal foci. Mediastinitis now occurs most frequently as a postoperative infection after median sternotomy. Regardless of the pathogenesis of infection, a high index of suspicion must be maintained for this infection so that aggressive, potentially lifesaving measures can be promptly initiated. Chronic mediastinitis, also known as *fibrosing, sclerosing,* or *granulomatous mediastinitis,* is a rare disorder often caused by *Histoplasma capsulatum.*

ANATOMIC CONSIDERATIONS

Detailed descriptions of mediastinal anatomy are available[1,2]; a few fundamental points are emphasized in this chapter. The mediastinum is the region within the thorax between the pleural sacs (Fig. 85.1). It extends from the diaphragm inferiorly to the superior aperture of the thorax. The sternum and costal cartilages make up the anterior boundary, and the 12 thoracic vertebral bodies border the mediastinum posteriorly. The mediastinum is arbitrarily divided into four subdivisions: superior, posterior, anterior, and middle. Structures within the mediastinum include the heart and great vessels, esophagus, distal portion of the trachea and mainstem bronchi, vagus and phrenic nerves, thymic remnants, and thoracic duct. These structures are surrounded by adipose tissue, loose connective tissue, and lymph nodes.

The mediastinum communicates with the structures of the head and neck via several fascial planes and potential spaces (see Chapter 64). The three major routes by which head and neck infections spread to the mediastinum are (1) the pretracheal space, (2) the long fascial planes of the posterior neck, and (3) the viscerovascular or lateral pharyngeal space. The long fascial planes of the posterior neck extend from the base of the skull to the diaphragm and include the retropharyngeal or retrovisceral space, the prevertebral space, and the danger space. In the preantibiotic era, Pearse[1] attempted to delineate the relative contribution of each route to the pathogenesis of mediastinitis and found the retropharyngeal space to be involved in 71% of cases, followed

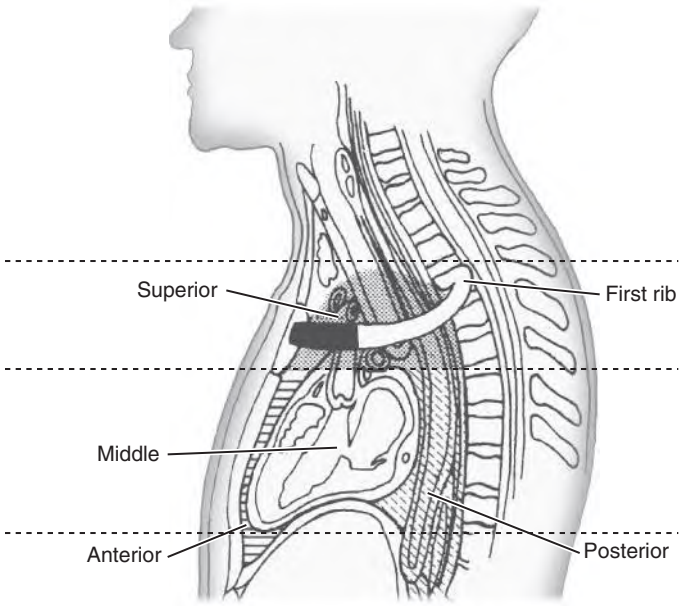

FIG. 85.1 Anatomic boundaries and divisions of the mediastinum.

by the lateral pharyngeal space in 21% and the pretracheal space in 8%.

ACUTE MEDIASTINITIS

Epidemiology and Pathogenesis

Primary infection of the mediastinum is rare. Essentially all cases of mediastinitis are due to the spread of infection from other sites or direct inoculation resulting from trauma or surgery. Table 85.1 summarizes the causes of mediastinitis; causes can be grouped into the following four categories: esophageal perforation, head and neck infection, infection originating at another site, and cardiothoracic surgery. The pathogenesis, clinical manifestations, and treatment vary according to the underlying cause of mediastinitis. Spontaneous pneumomediastinum is caused by alveolar rupture with air moving to the mediastinum, and is generally a benign condition not requiring antibiotics, surgical intervention, or often even hospitalization.[3]

Mediastinitis Secondary to Esophageal Perforation

Before the development of cardiac surgery, perforation of the esophagus was the leading cause of mediastinitis, followed by suppurative infections of the oropharynx.[1] In 1724 Boerhaave described the first case of mediastinitis caused by spontaneous rupture of the esophagus in a Dutch admiral who self-induced emesis.[4,5] This entity, known as *Boerhaave syndrome,* has continued to account for approximately 15% to 30% of cases of esophageal perforation.[6,7] Currently, esophageal perforation is most frequently due to iatrogenic injury.[6,7] Flexible fiberoptic endoscopy of the upper gastrointestinal tract is complicated by esophageal perforation in 0.074% to 0.4% of procedures.[7,8] The frequency of this complication increases with prior radiotherapy of the mediastinum and with interventions such as sclerotherapy, dilation, or esophageal stenting.[7,8] Swallowed foreign bodies, esophageal carcinoma, and nonsurgical trauma, such as transesophageal echocardiography, may also result in perforation of the esophagus and subsequent mediastinitis.[7,9,10]

The majority of esophageal perforations occur in the thoracic esophagus and are iatrogenic or spontaneous, whereas foreign-body injury is found predominantly in the cervical esophagus.[7,9,10] Depending on the site of esophageal perforation, mediastinitis may result from direct spillage of esophageal contents into the posterior mediastinum or the migration of contents, via the fascial planes of the neck, into the mediastinum. Spread of infection from the neck into the mediastinum is influenced by respiratory dynamics, in which the negative intrathoracic pressure generated during respiration tends to draw the infection into the mediastinum. A necrotizing chemical mediastinitis ensues, followed by a polymicrobial bacterial mediastinitis, which is often synergistic and necrotizing.

TABLE 85.1 Causes of Acute Mediastinitis

Esophageal Perforation
Iatrogenic
Esophagogastroduodenoscopy, esophageal dilation, esophageal variceal sclerotherapy, nasogastric tube, Sengstaken-Blakemore tube, endotracheal intubation, esophageal surgery including endoscopic resection, paraesophageal surgery, transesophageal echocardiography, transbronchial biopsy, anterior stabilization of cervical vertebral bodies, catheter ablation of atrial fibrillation
Swallowed Foreign Bodies
Bones, coins, can pull-tabs, drug-filled condoms, swords, ballpoint pens, button batteries
Trauma
Penetrating—gunshot wound, knife wound
Blunt—steering wheel injury, seatbelt injury, cardiopulmonary resuscitation, whiplash injury, barotrauma
Spontaneous or Other
Emesis, cricoid pressure during anesthesia induction, heavy lifting, defecation, parturition, carcinoma, ingestion of caustic or corrosive liquids
Head and Neck Infections
Odontogenic, Ludwig angina, pharyngitis, tonsillitis, parotitis, epiglottitis, Lemierre syndrome
Infection Originating at Another Site
Pneumonia; pleural space infection or empyema; subphrenic abscess; pancreatitis; cellulitis or soft tissue infection of the chest wall; osteomyelitis of sternum, clavicle, ribs, or vertebrae; hematogenous spread from distant foci
Lymph nodes: necrosis and hemorrhage (anthrax) or caseous necrosis (tuberculosis)
Cardiothoracic Surgery (Median Sternotomy)
Coronary artery bypass grafting, cardiac valve replacement, repair of congenital heart defect, heart transplantation, heart-lung transplantation, cardiac assist devices, extracorporeal membrane oxygenation, other types of cardiothoracic surgery

Mediastinitis Secondary to Head and Neck Infections or From Other Sites

Mediastinitis secondary to pharyngeal and odontogenic infections is often called "descending necrotizing mediastinitis or fasciitis," and before antibiotics were widely available, it accounted for 10% to 31% of mediastinitis cases.[1,11] Due to effective antimicrobials, these infections are now rare causes of mediastinitis. Middle-aged men predominate in most case series, with generally less than half of cases of descending necrotizing mediastinitis resulting from oral infections.[12] The remainder are due to pharyngeal or other cervical infections. The prototypic odontogenic infection leading to mediastinitis is Ludwig angina, which usually stems from an infection of the second or third mandibular molars spreading to involve the sublingual and submandibular spaces (see Chapter 64). From these spaces the infection can spread via the lateral pharyngeal space to involve the retropharyngeal space or carotid sheath and track into the mediastinum. During the antibiotic era, approximately 3.5% of cases of Ludwig angina have been complicated by mediastinitis.[13]

Mediastinitis resulting from infections involving the lateral pharyngeal space may originate from various sources, including the teeth, parotid glands, or tonsils, or, rarely, from otitis, mastoiditis, or epiglottitis.[12,14,15,16] Infections of the retropharyngeal space generally arise from perforation of the esophagus or by extension of pharyngitis, epiglottitis, or tonsillitis. These infections can easily spread into the superior mediastinum via the long fascial planes of the neck or, if the danger space is involved, into the posterior mediastinum. Not all patients with necrotizing

TABLE 85.2 Risk Factors for Surgical Site Infection/Mediastinitis Post–Cardiac Surgery

PREOPERATIVE RISK FACTORS	OPERATIVE RISK FACTORS	POSTOPERATIVE RISK FACTORS
Increasing age	Emergent surgery	Need for reexploration
Diabetes	Heart transplant	Prolonged ICU stay
Staphylococcus aureus nasal colonization	Increasing complexity of surgery	Need for mechanical ventilation >48 h
COPD	Use of internal thoracic arteries in CABG	Lack of perioperative glucose control
Peripheral vascular disease	Prolonged operative time	Placement of tracheostomy
Class 3–4 angina	Hair removal by razor, not clippers	Postoperative myocardial infarction
Renal failure requiring hemodialysis	Inappropriate timing of antibiotics	Receipt of multiple blood products
History of endocarditis	Prolonged time on cardiopulmonary bypass	
Cigarette smoking	High core temperature during bypass (>38°C)	
Low cardiac output		
Concurrent infection		
Prolonged preoperative hospitalization		
Preoperative use of a ventricular assist device		

CABG, Coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *ICU,* intensive care unit.

infections of the face and neck will progress to mediastinitis. Of 286 deep neck infections at a single center over 11 years, only 6% progressed to involve the mediastinum.[17] Petitpas and colleagues[18] evaluated risk factors for the development of mediastinitis and found that a pharyngeal source, administration of oral glucocorticoids, and the presence of gas in the tissue were associated with the development of mediastinitis.

Rarely, mediastinitis is due to spread from other adjacent infections. The pretracheal space descends into the anterior mediastinum and most often is involved in mediastinitis complicating procedures involving the thyroid and trachea.[1] Cases have been described secondary to the following conditions: pneumonia; pleural space infection; osteomyelitis of the ribs, clavicle, sternum, or vertebrae; subphrenic abscess; pancreatitis; cellulitis; and hematogenous seeding from distant foci.

Mediastinitis Secondary to Cardiothoracic Surgery

Cardiothoracic operations are among the most common surgical procedures performed in larger hospitals, and thus mediastinitis has become a predominantly postsurgical infection. Many studies have documented the incidence and risk factors for the development of mediastinitis after cardiothoracic surgery. In 1984 Sarr and colleagues[19] reviewed the available literature and found the incidence of mediastinitis to be 0.4% to 5% among patients undergoing median sternotomy. Since that time, numerous studies have been published, with incidence rates of 0.5% to 4.4%, with more recent studies showing incidence rates generally <2%.[20–22,23,24,25,26] Some selected trials evaluating rates of infection after cardiac surgery deserve mention as they suggest rates of infection may be declining. An analysis of 133,045 coronary artery bypass grafting (CABG) procedures reported to the National Healthcare Safety Network (NHSN) between 2006 and 2008 found that 1.3% developed a deep tissue or organ space infection, although not all of these infections involved the mediastinum.[27] The Society of Thoracic Surgeons National Cardiac Database, a voluntary quality reporting database that reportedly captures >95% of cardiac surgery cases, reported major infections occurred in 3.51% of more than 330,000 procedures in 2002–03, of which 25.1% was attributed to mediastinitis, with an overall incidence of mediastinitis of roughly 0.9%.[28] Data from this same database in 2016, including more than 217,000 procedures, demonstrated deep sternal wound infection/mediastinitis rates of 0.3%.[29] In outbreak settings the incidence of mediastinitis can be much higher, with rates of infection up to 23%.[30,31]

Risk Factors for Mediastinitis

Numerous factors that increase the risk of mediastinitis in cardiothoracic surgery have been identified. Most studies examining these risk factors are retrospective case-control studies and are limited by the problems inherent in retrospective surveys. Risk factors generally can be divided into the following categories: preoperative, intraoperative, and postoperative (Table 85.2). Risk factors that have been identified preoperatively include increasing age, diabetes mellitus, obesity, previous sternotomy, chronic obstructive pulmonary disease, peripheral vascular disease, class 3 or 4 angina, renal failure requiring hemodialysis, history of endocarditis, cigarette smoking, low cardiac output states, preoperative *Staphylococcus aureus* colonization, hair removal with razor versus removal with electric clippers, and prolonged preoperative hospitalization.[a] The contribution of each individual risk factor is difficult to ascertain, but obesity is one of the most consistent and strong predictors of mediastinitis. A body mass index of greater than 30 increases the risk of developing mediastinitis 2.2- to 6.5-fold.[b] The increased risk is likely multifactorial and may involve increased technical difficulties during surgery, prolonged operative time, increased bleeding, inadequate preoperative antibiotics, and increased risk of sternal dehiscence.[36,40] The contribution of gender to the risk of mediastinitis is unclear. A study of more than 18,000 CABG procedures performed in Norway found male gender to be associated with a 7.9-fold increase in mediastinitis risk, but analysis of NHSN data including more than 133,000 CABG procedures found female gender increased the risk of complex sternal wound infection, although only slightly (odds ratio [OR], 1.7).[26,27] The reasons for these differences are unclear.

Intraoperative and surgical risk factors identified include emergent surgery, heart transplant surgery, the complexity of surgery, use of one or both internal thoracic arteries in CABG, prolonged operative time, prolonged time on cardiopulmonary bypass, high core temperatures (>38°C) during cardiopulmonary bypass, indiscriminate use of electrocautery, and inappropriate timing of antibiotic prophylaxis.[c] The use of bone wax on sternal edges to decrease bleeding has been implicated as a risk factor for mediastinitis based on animal data, but a prospective, randomized study involving 400 patients undergoing CABG found no significant increase in mediastinitis associated with its use.[43,44] Of note, no clinical benefit was derived from its use either. The use of off-pump CABG surgery does not alter the incidence of mediastinitis, although minimally invasive procedures may have lower infection rates.[45,46] Postoperative risk factors that place patients at greater risk for mediastinitis include the need for reexploration to control bleeding, a prolonged length of stay in the intensive care unit, prolonged mechanical ventilation (>48 hours), tracheostomy placement, lack of perioperative and postoperative glucose control, postoperative myocardial infarction, and blood product transfusion.[d]

Despite much research, there is not universal agreement regarding any of these risk factors and their relative contribution. For example, despite nearly 40 years of surgical experience, debate still exists on whether the use of internal thoracic artery (ITA) grafts in CABG predisposes patients to mediastinitis. Use of the ITA for revascularization is preferred because graft patency rates and long-term survival are significantly higher than saphenous venous grafts.[49,50] However, in 1972, on the basis of anatomic studies of sternal blood supply, Arnold[51] suggested that the use of the ITA in CABG procedures might lead to significant sternal ischemia and predispose patients to sternal osteomyelitis and mediastinitis. This hypothesis has been supported by several laboratory and numerous clinical studies.[e] A review of studies published between 1997 and 2007 found the use of bilateral ITA grafts increased the risk of mediastinitis significantly, especially in diabetic patients.[53] A large randomized trial found bilateral ITA grafting was associated with twice the rate of sternal wound complications of unilateral grafting.[54] It should be noted that a number of other investigators have not observed any increase in sternal wound infections in patients undergoing CABG when one or both ITA grafts were used.[f] The surgical technique of skeletonized bilateral internal mammary artery grafting may abrogate

[a]References 20, 21, **23**, **24**, 25, **26**, **28**, **32**, 33, **34**, 35, **36**, 37, 38.
[b]References **23**, **24**, 25, **26**, **28**, **32**, **36**, 39.
[c]References 20, **23**, **24**, 25, **28**, **32**, **34**, 37, 38, 41, 42, **43**.
[d]References 20, 21, **23**, **24**, **26**, **32**, 39, 47, 48.
[e]References 20, 21, **24**, 25, **34**, **52**, 53.
[f]References **26**, **28**, **36**, 37–39, 55, **56**.

the increased risk of mediastinitis and could be a potential explanation for variability in findings.[53]

An increasing body of evidence has associated the receipt of blood products, particularly packed red blood cells (RBCs), with increased rates of postoperative bacterial infections, including mediastinitis. More than 20 years ago, Loop and colleagues[20] found the risk of mediastinitis increased with the number of units of blood transfused postoperatively, and more recently, Risnes and colleagues[26] noted a similar association between transfusion of multiple units of blood and mediastinitis. The authors of a systematic review of seven studies, including more than 32,000 cardiac surgery cases, concluded that RBC transfusion is associated with an increase in mediastinitis risk.[57] It appears this transfusion risk may be dose dependent and does not seem to apply to other blood products, such as fresh-frozen plasma (FFP) or platelets.[58,59] It is hypothesized that transfusion induces a downregulation of the immune response, predisposing to infection. On the basis of these data, routine transfusion at arbitrary hemoglobin levels should be avoided, and strategies to minimize transfusion should be used, such as the use of intraoperative cell saver and provision of FFP and platelets when bleeding occurs.

The use of mechanical support devices, including left ventricular assist devices and intraaortic balloon pumps, either before or after cardiac surgery, has been associated with an increase in the risk of mediastinitis.[28,34,60] Extracorporeal membrane oxygenation (ECMO) has increasingly been used for respiratory support either alone or in the cardiac surgery postoperative period, with large-vessel cannulation either in the femoral area or directly into the thoracic cavity. ECMO use after cardiac surgery has been noted to be a risk factor for mediastinitis in at least one study, and in a survey of 220 patients on ECMO, 64% developed a nosocomial infection with mediastinitis occurring in 11%.[25,61]

Patients undergoing heart transplantation are at higher risk for development of mediastinitis, with incidences of 2.1% to 8.7%.[62,63,64,65,66] Data on risk factors for mediastinitis in heart transplant patients are much more limited but include similar factors, such as obesity and prolonged cardiopulmonary bypass.[66,67] One risk factor particularly prevalent in heart transplant patients is the presurgical use of mechanical support devices, such as left ventricular assist devices or artificial hearts, which appear to increase the risk of mediastinitis.[64,65,68] There is debate regarding the effect of specific immunosuppressive agents on sternal wound infection and mediastinitis risk. Although Kuppahally and colleagues[67] found use of sirolimus to be a risk factor for posttransplant wound complications, including mediastinitis, Zuckermann,[66] in an analysis of three studies of everolimus, including more than 1000 heart transplants, did not find an increase in incisional complications when compared with other immunosuppressive regimens. Donor-to-recipient transmission of bacteria rarely has been observed to result in mediastinitis.[69]

Rates of mediastinitis in children undergoing cardiac surgery are generally lower than adults and range from 0.09% to 1.4%,[70,71–73] with the largest survey of 30,000 procedures in the United States noting mediastinitis in 0.3% of cases.[71] Although pediatric patients typically lack the chronic medical conditions predisposing adults to infection, some similar risk factors have been identified, including American Society of Anesthesiologists physical status classification class, previous cardiac procedure, preoperative hospitalization or ventilator use, complexity of surgery, duration of procedure, and receipt of multiple postoperative transfusions, which have all been associated with either increased risk of surgical site infection (SSI) or mediastinitis.[71,72,74,75] Risk factors unique to children include very young age (<90 days) and the presence of a genetic syndrome.[71–73,75] In pediatric patients, delayed sternal closure may predispose to development of mediastinitis, particularly due to gram-negative pathogens.[76,77]

Pathogenesis

It is believed that the pathogenesis of post–cardiac surgery mediastinitis is primarily due to the inoculation of organisms from the patient's endogenous bacterial microbiota or the surgical field into the operative site. Bacteria are able to propagate in the protected avascular area of the surgical wound and cause infection. The identification of risk factors, such as the length of time of surgery, the complexity of surgery, and the need for reexploration, all of which increase the likelihood of contamination, support this hypothesis, as does the observation of lower rates of wound infection and mediastinitis in patients undergoing cardiac surgery with minimally invasive techniques.[21,46] Outbreaks of mediastinitis that have been epidemiologically linked to sources such as bacteria from a particular surgeon's hands or nares also lend support to the concept of direct inoculation of the wound.[78]

The specific source of the bacterial contamination is usually the patient's own endogenous microbiota, particularly if that patient is colonized with *S. aureus.* In 1959 Weinstein noted patients colonized with *S. aureus* had a fourfold higher SSI rate and through phage typing was able to demonstrate that *S. aureus* isolates causing SSI were usually identical to those isolated from the patient's nares preoperatively.[79] Later, Jakob and colleagues[r] used pulsed-field gel electrophoresis (PFGE) to show *S. aureus* mediastinitis isolates were identical to those that had been obtained preoperatively from the nares of patients. Through culturing the nares of medical personnel, they were also able to show that health care workers were rarely the source of *S. aureus,* although two vein–harvest site infection isolates were identical to an isolate from a ward nurse.

Pathogenic mechanisms and ability to cause disease may vary depending on the infecting organism. Certain strains of coagulase-negative staphylococci may be particularly adapted to causing mediastinitis in the postoperative period. Archer and Armstrong[80] showed that patients are colonized by small numbers of antibiotic-resistant, coagulase-negative staphylococci, which become the predominant species when subjected to the selective pressure of prophylactic antibiotics. In addition, Olsson and colleagues[81] noted coagulase-negative staphylococci isolated from deep sternal wounds were more likely to produce biofilm. Mechanism of disease may differ even between methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA). A multivariate analysis of postoperative mediastinitis found differing risk factors for infection caused by each organism, with obesity being the only risk factor for MSSA mediastinitis, whereas being female, age older than 70 years, and having diabetes were risk factors for MRSA infection.[82] Preoperative nasal colonization with *S. aureus* has been associated with the development of mediastinitis.[35] A more recent analysis using PFGE of nasal and clinical isolates of *S. aureus* from patients with post–cardiac surgery mediastinitis found MSSA strains isolated from the mediastinum were identical to nasal strains in seven of nine cases.[83] No nasal MRSA isolates were isolated from the patients with mediastinitis resulting from MRSA, and all mediastinal MRSA isolates were highly genetically related, suggesting a possible nosocomial source.

Various immunosuppressive effects of cardiopulmonary bypass that may contribute to the pathogenesis of mediastinitis after surgery have been elucidated, although no difference in infectious complications, including mediastinitis, was observed when comparing CABG with and without the use of a cardiopulmonary bypass pump.[22,84] The importance of environmental and postoperative factors has also been emphasized by outbreaks of mediastinitis that have been linked to various sources, including contaminated tap water, air with increased concentrations of *Aspergillus fumigatus* spores, use of heater-cooler units colonized with nontuberculous mycobacteria, and poor hand-washing technique during postoperative care.[30,31,85,86,87] Controlled prospective studies are necessary to define better the factors that influence post–cardiac surgery mediastinitis.

Bacteriology

The bacteriology of mediastinitis complicating cardiovascular surgery is strikingly different from mediastinitis secondary to head and neck infections or esophageal perforations (Table 85.3). Mediastinitis secondary to cardiothoracic surgery is primarily caused by gram-positive cocci and less often by gram-negative bacilli. The relative contribution of *S. aureus* and MRSA varies by series, with two recent reviews of more than 500 cases of mediastinitis implicating *S. aureus* in roughly 60%,[88,89] whereas other reviews have found coagulase-negative staphylococci to be the most frequently isolated organisms.[90,91] Improved microbiologic techniques have increasingly implicated *Cutibacterium acnes* as an etiologic agent, but the role of this organism in mediastinitis requires further study.[90,91] *Candida* is responsible for a growing number of cases

TABLE 85.3 Microbiology of Mediastinitis

Organisms Frequently Recovered in Mediastinitis Secondary to Infection of the Head and Neck or Esophageal Perforation

Anaerobic

Gram-positive cocci—*Peptostreptococcus* spp.
Gram-positive bacilli—*Actinomyces, Eubacterium, Lactobacillus*
Gram-negative cocci—*Veillonella*
Gram-negative bacilli—*Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., *Porphyromonas* spp.

Aerobic or Facultative

Gram-positive cocci—*Streptococcus* spp., *Staphylococcus* spp.
Gram-positive bacilli—*Corynebacterium*
Gram-negative cocci—*Moraxella*
Gram-negative bacilli—Enterobacteriaceae, *Pseudomonas* spp., *Eikenella corrodens*
Fungi—*Candida albicans*

Representative Organisms Recovered in Mediastinitis Secondary to Cardiothoracic Surgery, With Representative Rate and Range

Gram-Positive Cocci

Staphylococcus aureus, 25% (7.1%–66.7%)
Staphylococcus epidermidis, 30% (6%–45.5%)
Enterococcus spp., 10% (8%–18.8%)
Streptococcus spp., 2% (0%–18.2%)

Gram-Negative Bacilli

Escherichia coli, 5% (0%–12.5%)
Enterobacter spp., 10% (4%–21.4%)
Klebsiella spp., 3% (0%–21.1%)
Proteus spp., 2% (0%–7.1%)
Other Enterobacteriaceae, 2% (0%–20%)
Pseudomonas spp., 2% (0%–54%)

Fungi

C. albicans, <2% (0%–20.5%)
Polymicrobial, 10% (0%–40%)

Others Occasionally Reported

Acinetobacter, Salmonella spp., *Legionella* spp., *Bacteroides fragilis, Corynebacterium* spp., *Burkholderia cepacia, Mycoplasma hominis, Candida tropicalis, Aspergillus* spp., *Nocardia* spp., *Kluyvera, Gordonia sputi, Mycobacterium fortuitum, Mycobacterium chelonae, Rhodococcus bronchialis*

Other Unusual Causes of Mediastinitis

Anthrax, brucellosis, actinomycosis, paragonimiasis, *Streptococcus pneumoniae*

FIG. 85.2 Mediastinitis. Chest radiograph shows large pneumomediastinum and pneumopericardium *(arrows)* in a patient with mediastinitis.

of mediastinitis after cardiothoracic surgery and may be associated with increased mortality.[92,93]

The bacteriology of mediastinitis due to esophageal perforation and extension of head and neck infections is frequently polymicrobial. Synergistic infection comprising both oral anaerobes and gram-negative bacilli is usually present. The most frequently isolated organisms include viridans group streptococci; staphylococci, including *S. aureus*; peptostreptococci; *Bacteroides* spp.; *Prevotella* spp.; and *Fusobacterium.* The relative frequency with which these organisms are isolated varies because of the difficulty in obtaining reliable anaerobic culture data.[94]

Clinical Manifestations and Diagnosis

The clinical manifestations of mediastinitis differ according to the underlying cause of disease. When mediastinitis occurs due to extension of an odontogenic or pharyngeal infection, the symptoms and signs of the primary infections predominate, such as pain, odynophagia, skin erythema, fever, and swelling of the affected site. Esophageal perforation may be clinically obvious or inapparent depending on the nature of the injury. Early in the course of mediastinitis, the signs and symptoms may be subtle, but as the condition progresses, patients note increasing chest pain, respiratory distress, and odynophagia. Chest pain is often the most prominent symptom and may localize depending on the portion of the mediastinum involved. In anterior mediastinitis, pain is often located in the cervical or substernal region. Pain from posterior mediastinitis may localize to the epigastric area with radiation to the interscapular region.[11] Patients with Boerhaave syndrome (transmural perforation of the esophagus) typically present with excruciating anterior chest pain with a history or severe vomiting or retching. Pleural effusion is a common complication and may manifest as pleuritic chest pain. Retroperitoneal extension may be accompanied by acute abdominal signs and may prompt unnecessary exploratory laparotomy.

Examination frequently reveals fever; tachycardia, crepitus, and edema of the chest or neck may also be present. *Hamman sign,* a crunching, rasping sound heard over the precordium synchronous with the cardiac rhythm, caused by emphysema of the mediastinum, may be audible in 50% of patients with pneumomediastinum.[95] The heart sounds may be distant and dull. In the later stages of mediastinitis, signs of bacteremia and sepsis may predominate. The early diagnosis of mediastinitis in an infant or neonate can be particularly challenging. A peculiar, interrupted, staccato type of inspiration has been described in many patients.[96] The signs and symptoms of mediastinitis in older children are similar to those observed in adults.[97]

Laboratory testing usually reveals leukocytosis along with other signs of infection and potentially organ dysfunction. Radiographically, plain films of the chest may reveal mediastinal widening, air-fluid levels, and subcutaneous or mediastinal emphysema (Fig. 85.2).[13] The lateral chest radiograph may be useful in showing superior mediastinal gas not evident on upright films. Complications of mediastinitis, such as pleural effusion or pneumoperitoneum, may also be evident.

Computed tomography (CT) is essential for diagnosis of mediastinitis in patients with odontogenic and pharyngeal infections. CT imaging of both the neck and chest are necessary to define the extent of the infection and determine if mediastinal involvement has occurred as this often alters the surgical approach. Typical CT findings include evidence of the primary infection along with mediastinal encapsulated fluid collections, air in soft tissue planes, pleural effusions, abscesses with air bubbles, and increased density of mediastinal fat with loss of typical tissue planes.[12,98,99] Transesophageal endosonography has been used to guide needle aspiration of the posterior mediastinum, particularly in cases in which the CT scan is inconclusive.[100] Technetium-labeled white blood cell scans have been reported to be helpful in the diagnosis of mediastinitis in specialized circumstances when CT scanning was not readily available.[101] Magnetic resonance imaging (MRI) has rarely been used, and its utility is unknown.

Chest radiographs in patients with esophageal perforation reveal significant abnormalities in about 90% of patients, although establishing the presence of a perforation can be difficult, and multiple modalities of imaging and direct visualization using endoscopy are often necessary to confirm the diagnosis.[102] Contrast esophagography using water-soluble contrast agents is recommended as the initial imaging examination and may reveal extravasation of dye. Although dilute barium provides better definition of anatomy and detection of subtle defects and perforations,

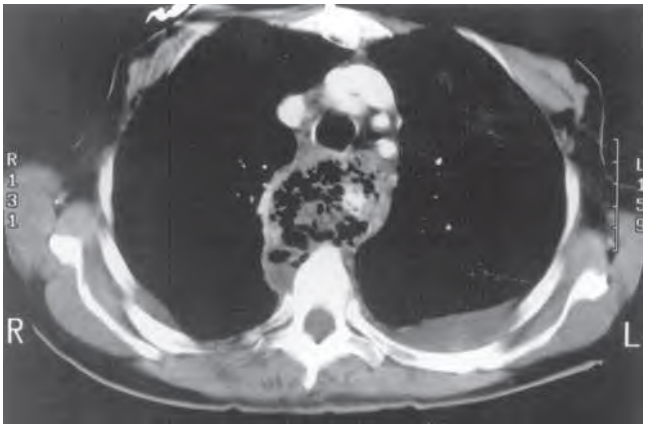

FIG. 85.3 Mediastinitis. Computed tomography scan of the chest at the level of the sixth thoracic vertebra shows large abscess within posterior mediastinum and left-sided pleural effusion. The patient had experienced perforation of the esophagus owing to a swallowed foreign body. *(From Rupp ME. Mediastinitis. In: Fishman AP, Elias JA, Fishman JA, et al, eds.* Fishman's Pulmonary Diseases and Disorders. *3rd ed. New York: McGraw-Hill; 1998:2036–2043.)*

it should generally be avoided because extravasated barium evokes significant inflammation.[7] CT is often helpful in both confirming the diagnosis and defining the extent of mediastinal contamination (Fig. 85.3), and some authors recommend the combination of both an esophagram and CT in all patients.[6,7,10] Upper endoscopy has been used both diagnostically to detect and evaluate the extent of injury and therapeutically to repair small injuries or remove foreign bodies.[10,103,104]

Mediastinitis Caused by *Bacillus anthracis*

The intentional release of *Bacillus anthracis* via the US Postal Service generated great interest in the recognition, management, and prevention of inhalational anthrax (also see Chapter 207). Inhalational anthrax exposure results in a hemorrhagic mediastinitis.[105] After inhalation, the 1- to 5-µm spores of *B. anthracis* are ingested by macrophages and transported to hilar and mediastinal nodes, where they germinate, propagate, and release toxins that lead to hemorrhage, edema, and necrosis. Approximately 90% of patients with inhalational anthrax exhibit mediastinal adenopathy or widening on radiographic studies.[105] The finding of mediastinal adenopathy or widening in a febrile patient should trigger strong suspicion for inhalational anthrax and institution of appropriate diagnostic and therapeutic measures.

Cardiac Surgery–Related Mediastinitis

Post–cardiothoracic surgery mediastinitis typically becomes clinically evident within 2 to 4 weeks after surgery, although rare instances occurring more than 1 year after surgery have been reported.[g] Infection resulting from gram-negative organisms may manifest earlier after surgery, typically within 2 weeks.[89] A review of 197 cases of mediastinitis found septic shock was more common in early-onset mediastinitis, as were enterococci and gram-negative pathogens, whereas *S. aureus* was the dominant pathogen after 14 days.[89] Usually, *S. aureus* mediastinitis is readily diagnosed on clinical grounds, whereas less virulent coagulase-negative staphylococci often have much subtler findings and may be initially misdiagnosed as uninfected in up to 30% of cases.[90]

In post–cardiac surgery patients the presentation of mediastinitis may be fulminant or subtle. Clinicians must have a high sensitivity for this infection in postoperative patients because they can present without localizing signs or symptoms, and the signs of sepsis may be the only evidence of infection.[19,89] Fever is the most common presenting symptom and may be accompanied by localized signs of infection, such as erythema, cellulitis, or purulent discharge from the mediastinal wound.[h] Patients may experience greater-than-normal postoperative pain, which can be pleuritic in nature. Sternal instability, dehiscence, and wound drainage are frequently noted and may be the only sign of infection in patients.[91] Dysphagia, the observation of bubbles emanating from the sternal wound, and chest wall emphysema are uncommon. Poststernotomy mediastinitis manifesting as a deep neck abscess without abnormal findings on chest examination has been reported, as has the development of septic shock and bacteremia without obvious signs of sternal infection.[89,107]

Laboratory tests usually show a moderate leukocytosis with a leftward shift of the white blood cell differential count. Biologic markers such as C-reactive protein and procalcitonin are typically elevated. Procalcitonin has been shown to be superior to C-reactive protein in diagnosing infection in patients having undergone cardiopulmonary bypass but has not been specifically studied in mediastinitis.[108] The presentation of mediastinitis in transplant patients may be atypical and lack the usual clinical findings of fever and elevated white blood cell count.[64] Procalcitonin has been found to be particularly useful in differentiating infection from rejection in transplant patients and may play an adjunctive role in the diagnosis of mediastinitis in this patient population.[109] Blood cultures are of variable usefulness in diagnosing mediastinitis. Patients with mediastinitis caused by *S. aureus* and gram-negative bacteria are frequently bacteremic. Post–cardiac surgery patients with bacteremia in which the source is not evident should be evaluated for possible mediastinitis because one author found the presence of *S. aureus* bacteremia in the first 60 days after median sternotomy had a 90% positive predictive value for mediastinitis.[110] Blood cultures are less useful in diagnosing mediastinitis caused by coagulase-negative staphylococci with rates of bacteremia typically less than 10%.[91]

Radiographically, mediastinal widening is a rare finding on plain chest films, and routine radiographs are usually of little value in the diagnosis of mediastinitis after cardiothoracic surgery (due to postsurgical abnormalities).[19,111] CT is usually the first diagnostic step when concern for postoperative mediastinitis exists, particularly when there is a need to differentiate superficial wound infections from deeper retrosternal processes. Characteristic findings include soft tissue swelling, pleural or pericardial effusions, fluid or air collections (or both), and sternal erosion.[111] Normal postoperative collections of fluid and gas are sometimes difficult to differentiate from early signs of mediastinitis, especially in the early postoperative period (<2 weeks).[111] The ability of CT to diagnose mediastinal infection was evaluated in 203 patients with mediastinitis and was found to have an overall sensitivity and specificity of 87.6% and 90.5%, respectively, and was particularly sensitive for detection of sternal osteomyelitis.[112] Dressler syndrome can be difficult to distinguish from mediastinitis after cardiac surgery by CT. The diagnostic value of nuclear scans has been espoused by several investigators and may be particularly useful when other imaging is equivocal.[113,114]

Browdie and colleagues[115] evaluated the relative value of CT, indium-111–labeled leukocyte scanning, and epicardial pacer wire cultures in 24 patients undergoing evaluation for possible mediastinitis and found that epicardial pacer wire cultures were 100% sensitive and 92% specific. Other authors have disagreed with the usefulness of epicardial pacer wire cultures. Two large studies, including more than 2000 patients, found routine pacer wire culture to be associated with an unacceptably high rate of false-positive findings.[116,117] In these two investigations the sensitivity and specificity of routine epicardial wire cultures ranged from 52.1% to 75% and 72.1% to 83.4%, respectively. Positive predictive values were 8.2% to 11.6%, and negative predictive values were 96.9% to 99.1%, suggesting that routine epicardial pacer wire cultures should not be obtained, but in cases where mediastinitis is a concern, they may have a role.[116,117] The usefulness of MRI and positron emission tomography (PET) scanning are not well defined, and MRI may be contraindicated when ferromagnetic metals are present in sternal wires, artificial heart valves, cardiac pacemakers, or vascular clips.

Several investigators have found mediastinal needle aspiration to be useful in the diagnosis of mediastinitis.[19,118] This method seems to be particularly useful for early diagnosis of mediastinitis before clinical symptoms make the diagnosis obvious, and it has been associated with improved clinical outcomes.[118]

[g]References 19, **23**, **32**, 37, **89**, 91, 106.
[h]References 19, 91.

Therapy

Therapy that includes medical and surgical techniques should be promptly initiated when mediastinitis is diagnosed along with aggressive nutritional and supportive care.

Mediastinitis Due to Esophageal Perforation

The principles of managing mediastinitis due to esophageal perforation include restoration of esophageal continuity, control of mediastinal contamination, and treatment with antimicrobials. Barrett[119] is credited with documenting in 1946 the first successful treatment of mediastinitis resulting from esophageal perforation. Since then, experts have usually recommended immediate aggressive surgical drainage, débridement of any devitalized tissue, and repair of the perforation.[7,9,120] A variety of surgical techniques may be used in the treatment of esophageal perforation, ranging from primary repair, which is preferred when feasible, to esophageal exclusion or diversion, to complete esophagectomy, which is usually reserved for patients with significant esophageal pathology such as malignancy.[6,104,121]

Over the past two decades, there have been aggressive efforts to identify those patients who may benefit from a "nonoperative" management strategy. Recent literature suggests that preferred algorithmic approaches take into account the location, severity, and control of the esophageal leak, along with the presence of tumor and severity of illness, to determine the best strategy for esophageal repair.[104,122] Nonoperative management is usually preferred in well-contained disruptions of the esophagus with minimal symptoms and no evidence of clinical toxicity or those with perforations identified before major mediastinal contamination occurs.[6,10,104,121,122] Although termed a "nonoperative" strategy, many patients have feeding tubes surgically implanted, and CT-guided drainage of any abscesses is essential for directing antimicrobial therapy and resolving infection.

A major advancement in treatment of esophageal perforation has been the development of endoscopic therapies, such as retrievable esophageal stents and endoscopic clips. Clipping may be particularly useful with small perforations due to foreign bodies.[123,124] Deployment of expandable esophageal stents to treat esophageal rupture has been increasingly common, with 30% of patients with benign esophageal ruptures managed using stents in 2014, compared with 7% in 2007.[125] Recent data suggest stenting may be associated with improvements in outcomes. A systematic review of 267 esophageal perforations managed by esophageal stenting noted perforation healing was achieved in 85% of patients with an overall mortality of 11%.[126] A propensity-matched study comparing stenting with primary surgical repair for iatrogenic rupture found similar rates of continued leak between the two procedures, but stenting was associated with decreased mortality (43% vs. 4%), shorter length of stay, and earlier oral intake.[127] It should be noted that many patients who underwent stenting required drainage of extraluminal fluid collections, often by video-assisted thorascopic surgery (VATS). Children with esophageal perforation are usually successfully managed with conservative treatment with broad-spectrum antibiotics, nasopharyngeal aspiration, parenteral nutritional support, and drainage of any fluid collections.[128,129]

Mediastinitis Due to Head and Neck Infection

As in esophageal perforation-induced mediastinitis, cases secondary to descending odontogenic or pharyngeal infection require prompt and aggressive surgical intervention. There is some debate in the literature regarding the preferred surgical approach, but all authors agree that adequate surgical drainage and débridement of all infected areas is of primary importance. Some authors have suggested that a transthoracic approach is necessary in all cases, noting that transcervical drainage may be inadequate.[16] An analysis of 69 cases found significantly higher mortality in patients managed with only drainage via the neck (47% vs. 19%).[98] Recent evidence suggests that the surgical approach should be based on the extent of the infection. When infection is confined to the superior mediastinum, management using cervicotomy with transcervical mediastinal drainage is likely adequate.[15,130,131,132] If mediastinitis has spread below the carina, the chest cavity should be entered using either sternotomy, posterior thoracotomy, or a combination of transcervical and subxiphoid drainage, depending on the location and extent of the infection.[15,132,133] Successful management of descending necrotizing mediastinitis using VATS has been reported as well.[134] Sumi and coworkers[135] described a nonoperative approach of aggressive CT-guided drainage catheters of both the neck and thoracic cavity in 14 patients. No patients required subsequent surgery, and only one patient died. Further research is necessary before this approach can be routinely advocated.

Although the importance of supportive therapy and surgical intervention cannot be overemphasized in both these forms of mediastinitis, the administration of appropriate antimicrobials is an essential component of therapy. Empirical regimens should be chosen based on the underlying cause and cover the major pathogens listed in Table 85.3. Penicillin G has traditionally been the antibiotic of choice in the treatment of anaerobic infections originating above the diaphragm and continues to exhibit excellent activity against most oral anaerobic bacteria. However, oral anaerobes such as *Prevotella* and *Porphyromonas* spp. (formerly *Bacteroides* spp.) are increasingly resistant to penicillin G, with agents such as broad-spectrum β-lactam/β-lactamase combinations, metronidazole, clindamycin, or carbapenems generally used.

Gram-negative enteric bacilli are also often involved in mediastinitis and should be accounted for when choosing an initial empirical regimen. Thus regimens including a β-lactam/β-lactamase inhibitor, a broad-spectrum cephalosporin plus metronidazole or clindamycin, or a carbapenem are reasonable empirical options. Coverage for MRSA is rarely indicated, as only approximately 5% of infections are caused by *S. aureus*, and this is mostly MSSA. Antibiotic therapy should be specifically tailored to the infecting organisms after definitive culture results are available, but treatment directed against anaerobic oropharyngeal organisms should be continued because of the difficulty in obtaining reliable anaerobic cultures.[94] The duration of therapy, which may range from weeks to months, is determined by the virulence of the bacteria, host factors, adequacy of drainage and the patient's response to therapy.

Cardiac Surgery–Related Mediastinitis

The treatment of mediastinitis secondary to cardiac surgery requires aggressive surgical drainage and débridement, including removal of any infected or necrotic tissue and bone along with sternal wires and any other foreign material. Although a few cases have been successfully treated by percutaneous catheter drainage alone, this is not preferred.[136] Two general approaches have been used in the surgical management of mediastinitis after cardiac surgery: open techniques and closed techniques. Open techniques involve débridement of infected tissue and open packing of the wound with delayed closure. Disadvantages of open procedures include respiratory insufficiency secondary to a lack of mechanical support for the thorax, resulting in prolonged mechanical ventilation, delayed healing and closure of the surgical wound, and hemorrhage from exposed vessels.

Rather than using open packing, many surgeons now use vacuum-assisted closure (VAC) therapy, also called *negative pressure wound therapy* (NPWT), either as a primary closure technique or as a bridge between débridement and definitive flap closure. Multiple studies comparing the use of NPWT with conventional treatment have shown the use of NPWT is associated with fewer dressing changes needed, earlier sternal rewiring, decreased need for soft tissue flaps, more rapid sterilization of the mediastinum, more rapid C-reactive protein decline, shorter in-hospital stays, reduced sternal reinfection rates, and decreased costs compared with usual care.[137,138,139,140] At least three studies have found NPWT to be associated with decreased mortality compared with historical management of patients using conventional surgical techniques.[24,139,140] A meta-analysis of 22 nonrandomized trials of NPWT for deep sternal wound infection found it was associated with significantly lower mortality (risk ratio [RR], 0.40; 95% CI, 0.28 to 0.57) and recurrence (RR, 0.34; 95% CI, 0.19 to 0.59).[141] Although these findings strongly suggest VAC therapy may be superior to other forms of surgical management, randomized trials comparing the use of VAC devices with other treatment modalities have not been performed. Although expert guidelines suggest that NPWT be used whenever delayed sternal wound closure is anticipated, a systematic review of the literature concluded that although NPWT was "efficacious and viable," the evidence supporting it was still "weak," and randomized controlled trial data were necessary.[141,142]

The closed method of surgical management involves débridement of affected tissue, followed by immediate closure of the sternum. If residual infection remains after closure, postoperative irrigation through drainage tubes or Redon catheters within the mediastinum may be performed, although this has become less common.[i] Sternal closure may be accomplished through direct closure of the wound, with or without sternal rewiring, or by the advancement of a soft tissue flap, usually from the pectoralis muscle. Some authors have reported high rates of success using these techniques, with cure rates greater than 90%.[143,144] A variety of soft tissue flaps may be used to reconstruct the chest wall, but no comparative data are available to guide selection. The most commonly used flap is the pectoral, but rectus abdominus transposition can be used, and omental tissue flaps have been successful in patients who have failed other treatment modalities.[146–150] A single report of the successful use of an anterolateral thigh, free myocutaneous flap has been published.[151] Tissue flaps can be used in primary closure of sternal wounds or after a period of open management with either traditional dressing changes or, more commonly, the use of NPWT as a bridge to flap. The preferred surgical management of mediastinitis is currently unknown, nor is the ideal timing of sternal closure, because some studies suggest improved outcomes with early sternal closure, whereas others report high rates of local recurrence.[106,152]

Irrigants used in mediastinitis have included various antimicrobial and antiseptic solutions, including antiseptics such as povidone-iodine or Dakin solution, various antibiotics, and saline. These agents have been associated with various complications, including the emergence of resistant organisms, pericardial and tissue toxicity, and systemic absorption and toxicity.[153,154] The commonly used irrigant povidone-iodine has been associated with iodine toxicity, renal failure, metabolic acidosis, and seizures and should generally be avoided.[145,155]

The use of parenteral antibiotics remains a cornerstone of therapy, although alone they are insufficient. Empirical therapy should be directed against staphylococci, including methicillin-resistant staphylococci and gram-negative aerobic bacilli. When definitive culture results are available, antimicrobials should be targeted to the pathogens isolated. As with mediastinitis secondary to infection of the head and neck, the duration of therapy is determined by multiple factors, including extent of infection, adequacy of drainage/débridement, presence of bone involvement, retention of prosthetic material, and pathogen isolated. Whether patients with mediastinitis caused by methicillin-resistant staphylococci are more likely to have treatment failure is a subject of debate. MRSA SSIs have been associated with increased mortality and treatment costs.[156] Some studies have associated MRSA poststernotomy mediastinitis with prolonged time to sterilization of the mediastinum, increased treatment failure, and increased mortality compared with MSSA.[106,157,158] Other authors, after controlling for comorbidities, choice of empirical initial antimicrobial regimen, and surgical treatment modality, found the mortality of MRSA poststernotomy mediastinitis to be quite high but not significantly different from other organisms.[158,159]

There has been significant interest in alternative antiseptics, and studies have suggested that in recalcitrant cases packing of the wound with granulated sugar or honey can successfully eradicate sternal infection.[160,161] The exact mechanism by which these substances promote wound healing has not been proven but is hypothesized to be a combination of promotion of wound healing with inhibition of bacterial growth through changes in tissue water content, changes in osmolality, and direct antibacterial growth inhibition.[162] Although there is still interest in these alternatives, NPWT has supplanted much of their use in mediastinal wounds.[163]

Prevention of Mediastinitis After Cardiac Surgery

Because of the devastating nature of poststernotomy mediastinitis, prevention is crucial. Numerous guidelines have been published regarding prevention of SSI and mediastinitis in the post–cardiac surgery setting.[145,164,165,166] Chapter 313 contains a detailed description of the prevention of SSIs, but a few items specific to cardiac surgery warrant mention. The Surgical Care Improvement Project (SCIP), which began in 2004, focuses on decreasing SSIs through implementation of evidence-based practices. Although SCIP measures are focused primarily on antimicrobial prophylaxis, control of 6 a.m. postoperative blood glucose in CABG surgery is also included. Several studies have shown that the control of postoperative blood glucose levels to less than 200 mg/dL, particularly using intravenous insulin protocols, significantly decreases the risk of deep sternal wound infection even in nondiabetic patie nts.[167,168,169] This effect has been quite significant, with a 50% or greater decrease in infection rates noted.

Antibiotic prophylaxis has become common in cardiac procedures despite the lack of placebo-controlled studies documenting its efficacy. Many questions exist about the optimal agent, dose, timing, and duration for antimicrobial prophylaxis. Guidelines from the Society of Thoracic Surgeons and by the American Society of Health System Pharmacists, Infectious Diseases Society of America, Surgical Infection Society, and Society for Healthcare Epidemiology of America have attempted to synthesize the data.[164,170,171] There is general agreement that prophylactic antimicrobials should be provided to achieve maximal tissue levels at the time of incision by infusing them within 1 hour of incision.[164] Very large patients may need higher doses of antimicrobials to achieve adequate concentrations, and higher doses should be used in larger patients. Another important aspect of antimicrobial prophylaxis is maintaining adequate tissue levels and agents with short half-lives, such as cefazolin, which should be redosed if the procedure duration exceeds two half-lives of the agent (typically 4 hours with cefazolin). Cefazolin has generally been regarded as the drug of choice for prophylaxis, with other early-generation cephalosporins, such as cefuroxime, generally considered to be equivalent.[164,171,172] The role of vancomycin as a routine prophylactic agent in cardiovascular surgery is controversial. The advantages of vancomycin, such as coverage of resistant pathogens, such as MRSA and enterococcal species, must be weighed against its disadvantages, including long infusion times, possible histamine release syndrome, and risk of development of vancomycin resistance in enterococci and staphylococci. In a comparison of vancomycin, cefazolin, and cefamandole, Maki and associates[173] showed a significant reduction in postoperative wound infections in patients receiving vancomycin prophylaxis. This finding has been contradicted by two meta-analyses and a systematic review, all of which found vancomycin to be no better than β-lactam antibiotics for the prevention of deep sternal wound infections, and in fact, vancomycin use was associated with increased rates of sternal wound infection in one analysis.[174,175,176] Another disadvantage of vancomycin use as a single agent for prophylaxis is a lack of coverage for gram-negative organisms. It is unclear if the addition of an agent with gram-negative activity, such as an aminoglycoside, fluoroquinolone, or cephalosporin, is necessary, but their use may be prudent when there is concern regarding these pathogens.[164,171] On the basis of these data, vancomycin should be reserved for prophylaxis in patients who cannot receive β-lactams due to severe allergy or who are at high risk for, or known to be colonized with MRSA.

Studies evaluating the duration of antimicrobial prophylaxis have found no clinical benefit to exceeding 48 hours of use, and use of prophylactic antibiotics beyond this time period has been associated with the emergence of resistant organisms.[164,170,175,177] The optimal duration of surgical prophylaxis is unclear as there are conflicting data regarding duration. Two meta-analyses suggested >24 hours of antibiotics was superior to <24 hours in preventing deep sternal wound infections, and current expert guidelines recommend prophylactic antibiotics be continued no longer than 48 hours postoperatively.[145,164,170,175,178] In contrast to this, recent Centers for Disease Control and Prevention guidelines recommend that surgical antimicrobial prophylaxis be discontinued at the time of wound closure in all procedures, including cardiac surgery.[179]

The prominent role of *S. aureus* in mediastinitis has made it a frequent target for prevention. The use of intranasal mupirocin to prevent SSIs through elimination of *S. aureus* nasal colonization has been supported by multiple trials, and application before or at the time of surgery is recommended.[164,171,180,181,182] This intervention should be targeted to patients known to be colonized with any form of *S. aureus* and not limited to those colonized only with MRSA.[181,182] If *S. aureus* colonization

[i]References 19, 44, **88**, **143**, 144, **145**.

status is unknown, it is reasonable to apply universally. Vaccines against *S. aureus* with the goal of preventing infections such as postsurgical mediastinitis are currently under investigation. Unfortunately, a large randomized trial in cardiac surgery patients found that although immunogenic, vaccines did not reduce *S. aureus* infections or SSI and increased mortality in those who developed an *S. aureus* infection.[183]

The use of topical antibiotics, such as gentamicin or vancomycin, applied to sternal wounds is controversial. Routine application of vancomycin paste to the cut sternal edges on opening and closing was recommended in one expert guideline[145] based on retrospective studies and a single randomized trial.[184,185] Not all retrospective studies support its use, and a recent meta-analysis, although supporting topical use, suggested publication bias might be present, making its routine adoption questionable.[186,187] Recent interest has also focused on gentamicin-collagen sponges implanted just before wound closure. Four randomized controlled studies have been performed, but only 1 study showed a significant decrease in deep sternal wound infections.[188,189,190,191] When the findings of these 4 studies were combined using meta-analysis, rates of deep sternal wound infections were lower with use of gentamicin sponges (OR, 0.62; 95% CI, 0.39 to 0.97).[192] Another meta-analysis that also included 10 observational studies found a similar reduction in the rate of deep sternal wound infections.[193] Despite these findings, more data are necessary before these devices are routinely implemented because the only US randomized trial found no impact on SSI rates.[190]

Finally, NPWT for prevention of infection in closed and noninfected wounds is seeing increased use. Small retrospective analyses have suggested that the use of NPWT for 5 to 7 days immediately after surgery may decrease infection rates in those who are at high risk (obese, bilateral ITA use, etc.).[194,195] Randomized trials are needed before this can be routinely recommended.

Complications and Prognosis

Complications of mediastinitis are due to local spread of infection and the systemic results of severe infection. Patients with descending necrotizing mediastinitis may require tracheostomy for airway protection, and prolonged mechanical ventilation is not uncommon.[12,16] Extension of the infection into contiguous structures and spaces can occur, including the pericardial space, resulting in pericardial effusion and tamponade; the pleural space; costochondral cartilages; and the peritoneum, resulting in peritonitis. Other major complications of mediastinitis, particularly after cardiac surgery include sternal osteomyelitis and sternal dehiscence or fracture.

An uncommon complication of mediastinitis after median sternotomy is an indolent costochondritis of one or more ribs, presenting as a localized swelling, erythema and pain. Débridement of necrotic cartilage maybe needed for cure.

Before the development of modern surgery and antibiotics, mediastinitis, from esophageal perforation, was regarded as uniformly fatal. With Barrett's first successful surgical repair of the esophagus in 1946,[119] morbidity and mortality decreased significantly but remains high. A national study in the United Kingdom between 2001 and 2012 showed that 30-day mortality decreased from 37% to 25%.[196] More recent studies using rapid diagnosis and a mix of surgical and nonsurgical treatments, including esophageal stenting, have demonstrated further declines in mortality (8%–12%), although outcomes vary depending on the nature of the rupture and management strategy used.[j] It is difficult to separate the influence that the nature of the injury and management strategy have on outcomes as they are often intertwined. General predictors of mortality in esophageal perforation include the presence of comorbidity, respiratory failure or signs of sepsis at diagnosis, malignant perforation, and a delay of more than 24 hours in initiation of therapy.[k] Rapidly recognized iatrogenic injuries managed by stenting may have mortality rates that are less than 5%.[10,104,198] The mortality associated with mediastinitis from head and neck infections, although still high, has declined with recent case series documenting mortality rates of 11% to 16%.[15,16,132,133] Specific prognostic factors in this form of mediastinitis have not been identified, but delays in diagnosis, severity of illness at presentation, and extension of the infection into the lower mediastinum may portend a worse outcome.[132,133,199]

Older studies in poststernotomy mediastinitis patients reported mortality rates of 30% to 50%, but more recent studies have described lower early mortality rates, often less than 10%, with some series reporting rates less than 5%.[l] This improvement in mortality rates is likely multifactorial, although a meta-analysis of NPWT suggested that it may be one of the major factors contributing to this improvement.[141] Although post–cardiac surgery mediastinitis is associated with an increase in postoperative mortality, there is debate in the literature regarding the long-term impact of this complication on mortality. Cayci and colleagues[201] found the development of deep sternal wound infection, after an initial increase in early mortality, did not alter long-term survival when preoperative, intraoperative, and postoperative risk factors were accounted for. Contrasting this, in 18,532 CABG procedures with a median of 10.4 years of follow-up, Risnes and coworkers[26] found mediastinitis was not associated with an increase in 30-day mortality but did result in a 59% increase in long-term mortality. An important factor in determining outcome is the length of time between diagnosis and initiation of definitive surgical and antimicrobial therapy, and delays are associated with worse outcomes.[106] Other prognostic indicators associated with increased mortality include advanced age, presence of significant underlying medical comorbidities, bacteremia, early-onset mediastinitis, mediastinal infection due to *Candida* spp. or MRSA, need for prolonged mechanical ventilation, need for intraaortic balloon pump, and cytomegalovirus shedding. [m]

In examining the economic ramifications of mediastinitis, Loop and coworkers[20] found the hospital charges of patients undergoing CABG who experienced mediastinitis were 280% greater than patients with uncomplicated bypass surgery, and the median length of stay ranged from 38 to 51 days. Other studies have reported that poststernotomy mediastinitis results in excess hospital stays of 12 to 30 days and a twofold to threefold increase in cost of care.[32,37,43,204] Because many of these infections are regarded as "preventable," beginning in 2008 the US Centers for Medicaid and Medicare Services stopped reimbursing hospitals for additional costs associated with postoperative mediastinitis. Data from the first 2 years after policy implementation showed alterations in coding but no measurable reduction in the rates of postoperative mediastinitis.[205]

CHRONIC/FIBROSING MEDIASTINITIS

Definition and Etiology

The terms *fibrosing, sclerosing,* and *granulomatous mediastinitis* refer to a chronic form of mediastinitis characterized by an invasive and compressive inflammatory mediastinal infiltrate. The first report of this entity, which may cause 10% of all primary mediastinal masses,[206] was a description by Ulmont in 1855.[207] Although the underlying pathophysiology of fibrosing mediastinitis has remained obscure, many authorities believe the majority of cases are secondary to infection with *H. capsulatum*. With careful analysis, 73% of cases previously characterized as nonspecific granulomatous mediastinitis were reclassified as secondary to *H. capsulatum* infection by restaining of the tissue with fungal stains and a thorough review of the pathologic sections.[208,209] A recent case series found 84% of patients with fibrosing mediastinitis had serologic, pathologic, or radiologic findings consistent with histoplasmosis.[210] Other infectious etiologies have been described, including, most frequently, tuberculosis,[211] and, more rarely, actinomycosis,[212] nocardiosis,[213] blastomycosis, coccidioidomycosis,[214] aspergillosis,[214] *Conidiobolus, Rhizopus* spp. and other causes of mucormycosis,[215,216] and *Wuchereria bancrofti* infection.[217] Older literature often lists syphilis as a prominent cause of granulomatous mediastinitis; however, this was based on seropositivity without other supporting evidence. Other conditions that closely mimic this entity include sarcoidosis, silicosis, lymphoma, mesothelioma, Behçet disease, mediastinal fibrosis associated with radiation, Riedel struma, and sclerosing cholangitis.[214,218–221] Some cases of fibrosing mediastinitis are likely a manifestation of other unusual

[j]References **7**, **10**, 103, **122**, 126, **127**.
[k]References **7**, **9**, **104**, **121**, 194, 197.
[l]References 20, **24**, 146, **163**, 200.
[m]References **88**, **89**, 93, 139, 157, 202, 203.

systemic fibroinflammatory disorders, including idiopathic retroperitoneal fibrosis, immunoglobulin (Ig)G4-related disease, or even mast cell activation syndrome.[222–224]

Manifestations and Diagnosis

Many patients with fibrosing mediastinitis are asymptomatic and come to medical attention when chest imaging incidentally reveals a mediastinal mass. When symptoms occur, they are usually related to invasion or obstruction of structures within or adjacent to the mediastinum (Table 85.4). The most common complaints at presentation are cough, dyspnea, chest pain, exercise intolerance, and hemoptysis.[210] Fibrosing mediastinitis is the most common nonmalignant cause of superior vena cava syndrome,[225] and patients typically present with plethora and edema of the face, neck, and upper torso; neck vein distention; headache; and visual disturbances. Obstruction of the pulmonary arteries results in cough, dyspnea, and symptoms consistent with right-sided heart failure. Pulmonary infarction, although rare, has been reported to occur in patients with fibrosing mediastinitis.[226] Pulmonary venous obstruction causes patients to experience a "pseudo–mitral stenosis syndrome" with exertional dyspnea, easy fatigability, and occasional hemoptysis. Patients with airway obstruction may present with cough, wheezing, dyspnea, hemoptysis, or recurrent episodes of bacterial bronchitis or pneumonia. Patients complaining of dysphagia may have esophageal obstruction secondary to posterior extension.

Findings on chest radiograph may be subtle, but most patients have mediastinal widening; other common radiographic findings include hilar mass, mediastinal calcification, and evidence of superior vena cava obstruction. CT is the preferred modality for evaluating fibrosing mediastinitis, and findings typically reveal one of two patterns. The most common finding is a focal, infiltrating mediastinal mass within the superior mediastinum, often with calcifications, which is most commonly on the right side.[210,227,228] Many authors believe this pattern is secondary to histoplasmosis or other infectious etiologies. The second pattern is characterized by diffuse mediastinal infiltration without prominent calcifications and may be more typical of noninfectious etiologies. CT is also useful for defining the extent of compression of mediastinal structures, with the exception of the esophagus, which is better imaged using an esophagram. Two large case series found vascular narrowing (39%–48%), especially the superior vena cava (20%–39%), to be the most commonly obstructed structures, followed by bronchial (27%–33%) and esophageal (3%–9%).[210,227] Magnetic resonance angiography offers little advantage over CT but along with pulmonary arteriography may be helpful in the assessment of the pulmonary vascular integrity.[229,230] Ventilation-perfusion lung scans often reveal large perfusion defects secondary to obstruction of the pulmonary vessels. PET scans, although not routinely indicated in fibrosing mediastinitis, are often used for evaluation of mediastinal mass lesions and may show increased metabolic activity suspicious for a malignancy.[210,230]

The diagnosis of fibrosing mediastinitis usually requires pathologic examination. Adequate tissue sampling is crucial in ruling out causes such as nodular sclerosing Hodgkin disease and sclerosing variants of non-Hodgkin lymphomas. The histologic appearance of fibrosing mediastinitis reflects a continuum of findings that range from predominantly granulomatous lesions with significant inflammation to minimally cellular fibrosing masses without inflammation.[210,221] Lesions noted may include caseating granulomas but typically are extensive paucicellular, densely hyalinized, collagenous tissue infiltrating and obliterating mediastinal adipose tissue, and structures with varying amounts of lymphocytes and mononuclear cells. Specific stains for fungi may reveal organisms consistent with *Histoplasma,* but cultures are usually negative.[206]

TABLE 85.4 Complications and Manifestations of Sclerosing Mediastinitis

Pulmonary venous or arterial obstruction
Superior vena cava obstruction
Inferior vena cava obstruction
Esophageal obstruction
Esophagobronchial obstruction
Tracheobronchial obstruction
Pulmonary venous or arterial obstruction
Pulmonary hypertension
Pulmonary infarction
Cor pulmonale
Thoracic duct obstruction
Constructive pericarditis
Coronary artery stenosis
Mediastinal nerve entrapment
Recurrent laryngeal nerve palsy

Pathogenesis

Fibrosing mediastinitis likely reflects a common immunologic end point of a heterogeneous group of inciting factors, and multiple mechanisms have been proposed to explain this condition. The findings of distinct radiographic and pathologic patterns of mediastinal disease suggest there may be multiple pathophysiologic mechanisms, although the most common mechanism is likely an immune-mediated hypersensitivity to *H. capsulatum* antigens possibly set off by the rupture of a caseous lymph node into the mediastinum.[206,210,227,228] A second similar hypothesis is the development of a delayed hypersensitivity reaction caused by the spread of soluble *Histoplasma* antigens into the mediastinum.[228] An alternative explanation proposes that fibrosing mediastinitis represents an abnormality of collagen production and organization similar to that of idiopathic retroperitoneal fibrosis, Riedel struma, or IgG4-related disorders leading to diffuse fibrosis without calcifications.[223,227,228] Either explanation is plausible, and the presence of a genetic predisposition and overlap between pathogenic mechanisms is possible. Supporting the role of genetic predisposition, a recent case-control study found histoplasmosis-associated fibrosing mediastinitis to be associated with human leukocyte antigen DQB1*04:02.[231]

Treatment

No controlled trials of medical or surgical therapy have been conducted in fibrosing mediastinitis. Patients without symptoms at the time of diagnosis may be safely managed with close monitoring, as demonstrated by 17 asymptomatic patients who were followed for a median of 68 months with none showing evidence of disease progression.[210] Despite the frequent finding of fungal organisms, little evidence supports the presence of an active infection at the time of diagnosis, and although antifungal therapies are frequently used (23 of 80 patients in one case series), the evidence supporting their efficacy is based on case reports of success only.[210,228,232] Surgical attempts to relieve vascular obstruction at the hilum can impede collateral flow around an obstructed superior vena cava. Case reports of success with corticosteroids have appeared, but their role in the treatment of fibrosing mediastinitis is minimal and likely limited to those where fibrosing mediastinitis is due to some other initiating condition, such as sarcoid or retroperitoneal fibrosis.[210,233] Despite a lack of efficacy, antifungal and antiinflammatory therapies are often used because no clearly efficacious treatment options exist. When medical therapy is provided, imaging and symptoms should be monitored, and patients without a clearly documented response should have therapy discontinued because it may result in toxicity and side effects. In small case series the selective estrogen receptor modulator tamoxifen was shown to improve idiopathic retroperitoneal fibrosis, leading some to use it in fibrosing mediastinitis with rare reports of success.[234,235] Tamoxifen's role as a treatment is unknown and may be limited to cases related to retroperitoneal fibrosis because estrogen and progesterone receptors have not been demonstrated to be present on cells mediating fibrosing mediastinitis.[221]

It is difficult to make recommendations regarding the timing or usefulness of surgical intervention due to the variable natural history of this disease because some patients progress to compression of vital structures, and others seem to have self-limited disease. Some have suggested that early surgical intervention with removal of granulomatous tissue may prevent the development of subsequent end-stage fibrosis, but the literature supporting this is scanty.[236] Due to the difficulty of the procedure and relatively high complication rates, surgical and nonsurgical interventions are generally reserved for patients who experience obstruction or invasion of mediastinal structures, leading to significant symptoms or cardiac complications. Despite the technical difficulties of surgical interventions, centers with experience have

published success rates of greater than 90%.[210] Recent advances in nonsurgical interventions have been used to relieve obstructions of the superior vena cava, pulmonary vessels, and bronchi. Although published success rates of relief of obstruction are somewhat lower than surgery (78%–80%), nonsurgical interventions avoid the significant morbidity associated with surgical interventions.[210,237] However, even nonsurgical interventions have been associated with high complication rates in patients with severe disease and have not been associated with improved clinical outcomes.[238] Regardless of the type of intervention, the progressive nature of the disease often means patients require multiple and progressive interventions over time. Although some patients with fibrosing mediastinitis will succumb to the disease, the overall prognosis is unknown, and outcomes may depend on the structures obstructed. Peikert and colleagues[210] used the Social Security Death Index database to follow up 80 patients with this disease for a median of 68 months (0–401 months) and found that, although 5 had died, only 2 deaths were specifically attributed to fibrosing mediastinitis. In contrast, 4 of 8 patients with pulmonary vein stenosis requiring intervention died within 4 weeks of their intervention, despite hemodynamic and symptomatic improvement.[238] There is some suggestion that bilateral mediastinal involvement, particularly when it involves the pulmonary veins, may be associated with increased mortality.[237,238]

Key References

The complete reference list is available online at Expert Consult.

6. Carrott PW, Low DE. Advances in the management of esophageal perforation. *Thorac Surg Clin*. 2011;21:541–555.
7. Brinster CJ, Singhal S, Lee L, et al. Evolving options in the management of esophageal perforation. *Ann Thorac Surg*. 2004;77:1475–1483.
9. Bhatia P, Frotin D, Inculet RI, et al. Current concepts in the management of esophageal perforations: a twenty-seven year Canadian experience. *Ann Thorac Surg*. 2011;92:209–215.
10. Kuppusamy MK, Hubka M, Felisky CD, et al. Evolving management strategies in esophageal perforation: surgeons using nonoperative techniques to improve outcomes. *J Am Coll Surg*. 2011;213:164–172.
15. Chen KC, Chen JS, Kuo SW, et al. Descending necrotizing mediastinitis: a 10-year surgical experience in a single institution. *J Thorac Cardiovasc Surg*. 2008;138:191–198.
16. Misthos P, Katsaragakis S, Kakaris S, et al. Descending necrotizing anterior mediastinitis: analysis of survival and surgical treatment modalities. *J Oral Maxillofac Surg*. 2007;65:635–639.
18. Petitpas F, Blancal JP, Mateo J, et al. Factors associated with the mediastinal spread of cervical necrotizing fasciitis. *Ann Thorac Surg*. 2012;93:234–239.
23. Abboud CS, Wey SB, Balter VT. Risk factors for mediastinitis after cardiac surgery. *Ann Thorac Surg*. 2004;77:676–683.
24. Baillot R, Cloutier D, Montalin L, et al. Impact of deep sternal wound infection management with vacuum-assisted closure therapy followed by sternal osteosynthesis: a 15-year review of 23,499 sternotomies. *Eur J Cardiothorac Surg*. 2010;37:880–887.
26. Risnes I, Abdelnoor M, Almdahl SM, et al. Mediastinitis after coronary artery bypass grafting risk factors and long-term survival. *Ann Thorac Surg*. 2010;89:1502–1510.
28. Fowler VG, O'Brien SM, Muhlbaier LH, et al. Clinical predictors of major infection after cardiac surgery. *Circulation*. 2005;30(suppl):I358–I365.
32. Filsoufi F, Castillo JG, Rahmanian PB, et al. Epidemiology of deep sterna wound infection in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2009;23:488–494.
34. Robinson PJ, Billah B, Leder K, et al. Factors associated with deep sternal wound infection and haemorrhage following cardiac surgery in Victoria. *Interact Cardio Vasc Thorac Surg*. 2007;6:167–171.
36. Eklund AM, Lyytikainen O, Klemets P, et al. Mediastinitis after more than 10,000 cardiac surgical procedures. *Ann Thorac Surg*. 2006;82:1784–1789.
37. Perrault LP, Kirkwood KA, Chang HL, et al. A prospective multi-institutional cohort study of mediastinal infections after cardiac operations. *Ann Thorac Surg*. 2018;105:461–468.
43. Hollenbeak CS, Murphy DM, Koenig S, et al. The clinical and economic impact of deep chest surgical site infections following coronary bypass graft surgery. *Chest*. 2000;118:397–402.
52. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, et al. The impact of deep sternal wound infection on long-term survival after coronary artery bypass grafting. *Chest*. 2005;127:464–471.
54. Taggart DP, Altman DG, Gray AM, et al. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2016;375:2540–2549.
56. Iribarne A, Westbrook BM, Malenka DJ, et al. Should diabetes be a contraindication to bilateral internal mammary artery grafting? *Ann Thorac Surg*. 2018;105:709–714.
63. Abid Q, Nkere UU, Hasan A, et al. Mediastinitis in heart and lung transplantation: 15 years' experience. *Ann Thorac Surg*. 2003;75:1565–1571.
64. Senechal M, LePrince P, du Montcel ST, et al. Bacterial mediastinitis after heart transplant: clinical presentation, risk factors, and treatment. *J Heart Lung Transplant*. 2004;23:165–170.
70. Al-Sehly AA, Robinson JL, Lee BE, et al. Pediatric poststernotomy mediastinitis. *Ann Thorac Surg*. 2005;80:2314–2320.
75. Kagan J, Lautenbach E, Bilker WB, et al. Risk factors for mediastinitis following median sternotomy in children. *Pediatr Infect Dis J*. 2007;26:613–618.
82. Ashley ESD, Carroll DN, Engemann JJ, et al. Risk factors for postoperative mediastinitis due to methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2004;38:1555–1560.
88. Trouillet JL, Vuagnat A, Combes A, et al. Acute poststernotomy mediastinitis managed with debridement and closed-drainage aspiration: factors associated with death in the intensive care unit. *J Thorac Cardiovasc Surg*. 2005;129:518–524.
89. Mekontso Dessap AM, Vivier E, Girou E, et al. Effect of time to onset on clinical features and prognosis of post-sternotomy mediastinitis. *Clin Microbiol Infect*. 2011;17:292–299.
101. Jakob HG, Borneff-Lipp M, Bach A, et al. The endogenous pathway is a major route for deep sternal wound infection. *Eur J Cardiothorac Surg*. 2000;17:154–160.
104. Schweigert M, Sousa HS, Solymosi N, et al. Spotlight on esophageal perforation: a multinational study using the Pittsburgh esophageal perforation severity scoring system. *J Thorac Cardiovasc Surg*. 2016;151:1002–1011.
108. Sponholz C, Sakr Y, Reinhart K, et al. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. *Crit Care*. 2006;10:R145–R156.
121. Abbas G, Schuchert MJ, Pettiford BL, et al. Contemporaneous management of esophageal perforation. *Surgery*. 2009;146:749–756.
122. Lindenmann J, Matzi Neuboeck N, et al. Management of esophageal perforation in 120 consecutive patients: clinical impact of a structured treatment algorithm. *J Gastointest Surg*. 2013;17:1036–1043.
127. Freeman RK, Herrera A, Ascioti AJ, et al. A propensity-matched comparison of cost and outcomes after esophageal stent placement or primary surgical repair for iatrongenic esophageal perforation. *J Thorac Cardiovasc Surg*. 2015;149:1550–1555.
132. Ridder GJ, Maier W, Kinzer S, et al. Descending necrotizing mediastinitis: contemporary trends in etiology, diagnosis, management, and outcome. *Ann Surg*. 2010;251:528–534.
141. Falagas ME, Tansarli G, Kapaskelis A, et al. Impact of vacuum-assisted closure (VAC) therapy on clinical outcomes of patients with sternal wound infections: a meta-analysis of non-randomized studies. *PLoS ONE*. 2013;8:e64741.
142. Raja S, Berg GA. Should vacuum-assisted closure therapy be routinely used for management of deep sternal wound infection after cardiac surgery? *Interact Cardiovasc Thorac Surg*. 2007;6:523–528.
143. Molina JE, Nelson EC, Smith RA. Treatment of postoperative sternal dehiscence with mediastinitis: twenty-four-year use of a single method. *J Thorac Cardiovasc Surg*. 2006;132:782–787.
145. Lazar HL, Salm TV, Englelman R, et al. Prevention and management of sternal wound infections. *J Thorac Cardiovasc Surg*. 2016;152:962–972.
159. Reddy SLC, Grayson AD, Smith G, et al. Methicillin resistant *Staphylococcus aureus* infections following cardiac surgery: incidence, impact, and identifying adverse outcome traits. *Eur J Cardiothorac Surg*. 2007;32:113–117.
163. De Feo M, Della Corte A, Vicchio M, et al. Is post-sternotomy mediastinitis still devastating after the advent of negative-pressure wound therapy? *Tex Heart Inst J*. 2011;38:375–380.
164. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70:195–283.
167. Kramer R, Groom R, Weldner D, et al. Glycemic control and reduction of deep sternal wound infection rates. *Arch Surg*. 2008;143:451–456.
170. Edwards FH, Engelman RM, Houck P, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part I: duration. *Ann Thorac Surg*. 2006;81:397–404.
171. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part II: antibiotic choice. *Ann Thorac Surg*. 2007;93:1569–1576.
175. Lador A, Nasir H, Mansur N, et al. Antibiotic prophylaxis in cardiac surgery: systematic review and meta-analysis. *J Antimicrob Chemother*. 2012;67:541–550.
176. Bolon MK, Morlote M, Weber SG, et al. Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. *Clin Infect Dis*. 2004;38:1357–1363.
181. Shrestha NK, Banbury MK, Weber M, et al. Safety of targeted perioperative mupirocin treatment for preventing infections after cardiac surgery. *Ann Thorac Surg*. 2006;81:2183–2188.
182. Bode LG, Kluytmans AJ, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med*. 2010;362:9–17.
185. Lazar HL, Ketchedjian A, Haime M, et al. Topical vancomycin in combination with perioperative antibiotics and tight glycemic control helps to eliminate sternal wound infections. *J Thorac Cardiovasc Surg*. 2014;148:1035–1040.
190. Bennett-Guerrero E, Ferguson TB, Lin M, et al. Effect of an implantable gentamicin-collagen sponge on sternal wound infections following cardiac surgery: a randomized trial. *JAMA*. 2010;304:755–762.
193. Kowalewski M, Pawliszak W, Zaborowska K, et al. Gentamicin-collagen sponge reduces the risk of sternal wound infections after heart surgery: meta-analysis. *J Thorac Cardiovasc Surg*. 2015;149:1631–1640, e6.
199. Kocher GJ, Hoksch B, Caversaccio M, et al. Diffuse descending necrotizing mediastinitis: surgical therapy and outcome in a single-centre series. *Eur J Cardiothorac Surg*. 2012;42:e66–e72.
201. Cayci C, Russo M, Cheema F, et al. Risk analysis of deep sternal wound infections and their impact on long-term survival: a propensity analysis. *Ann Plast Surg*. 2008;61:294–301.
205. Calderwood MS, Kleinman K, Soumerai SB, et al. Impact of Medicare's payment policy on mediastinitis following coronary artery bypass graft surgery in US hospitals. *Infect Control Hosp Epidemiol*. 2014;35:144–151.
210. Peikert T, Colby TV, Midthun DE, et al. Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response. *Medicine (Baltimore)*. 2011;90:412–423.
221. Flieder DB, Suster S, Moran CA. Idiopathic fibroinflammatory (fibrosing/sclerosing) lesions of the mediastinum: a study of 30 cases with emphasis on morphological heterogeneity. *Mod Pathol*. 1999;12:257–264.
228. Rossi SE, McAdams P, Rosado-de-Christenson ML, et al. Fibrosing mediastinitis. *Radiographics*. 2001;21:737–757.
231. Strock SB, Gaudieri S, Mallal S, et al. Fibrosing mediastinitis complicating prior histoplasmosis is associated with human leukocyte antigen DQB1*04:02—a case control study. *BMC Infect Dis*. 2015;15:206.
233. Seferian A, Steriade A, Jais X, et al. Pulmonary hypertension complicating fibrosing mediastinitis. *Medicine (Baltimore)*. 2015;94:e1800.
237. Albers EL, Pugh ME, Hill KD, et al. Percutaneous stent implantation as treatment for central vascular obstruction due to fibrosing mediastinitis. *Circulation*. 2011;123:1391–1399.
238. Ponamgi SP, DeSimone CV, Lenz CJ, et al. Catheter-based intervention for pulmonary vein stenosis due to fibrosing mediastinitis: the Mayo Clinic experience. *Int J Cardiol Heart Vasc*. 2015;8:103–107.

References

1. Pearse HE Jr. Mediastinitis following cervical suppuration. *Ann Surg*. 1938;108:588–611.
2. Chow AW. Life-threatening infections of the head and neck. *Clin Infect Dis*. 1992;14:991–1004.
3. Ebina M, Inoue A, Takaba A, et al. Management of spontaneous pneumomediastinum: are hospitalization and prophylactic antibiotics needed? *Am J Emerg Med*. 2017;35:1150–1153.
4. Boerhaave H. *Artocis, nec descripti prius Morbi Historia*. Secundem Artis Leges Conscripta: Lugdunis Batavorum Bouresteniana; 1724.
5. Barrett NR. Spontaneous perforation of the oesophagus. *Thorax*. 1946;1:48–70.
6. Carrott PW, Low DE. Advances in the management of esophageal perforation. *Thorac Surg Clin*. 2011;21:541–555.
7. Brinster CJ, Singhal S, Lee L, et al. Evolving options in the management of esophageal perforation. *Ann Thorac Surg*. 2004;77:1475–1483.
8. Bhatia NL, Collins JM, Nguyen CC, et al. Esophageal perforation as a complication of esophagogastroduodenoscopy. *J Hosp Med*. 2008;3:256–262.
9. Bhatia P, Frotin D, Inculet RI, et al. Current concepts in the management of esophageal perforations: a twenty-seven year Canadian experience. *Ann Thorac Surg*. 2011;92:209–215.
10. Kuppusamy MK, Hubka M, Felisky CD, et al. Evolving management strategies in esophageal perforation: surgeons using nonoperative techniques to improve outcomes. *J Am Coll Surg*. 2011;213:164–172.
11. Keefer CS. Acute and chronic mediastinitis. *Arch Intern Med*. 1938;62:109–136.
12. Roccia F, Percorari GC, Oliaro A, et al. Ten years of descending necrotizing mediastinitis: management of 23 cases. *J Oral Maxillofac Surg*. 2007;65:1716–1724.
13. Moreland LW, Corey J, McKenzie R. Ludwig's angina: report of a case and review of the literature. *Arch Intern Med*. 1988;148:461–466.
14. Guardia SN, Cameron R, Phillips A. Fatal necrotizing mediastinitis secondary to acute suppurative parotitis. *J Otolaryngol*. 1991;20:54–56.
15. Chen KC, Chen JS, Kuo SW, et al. Descending necrotizing mediastinitis: a 10-year surgical experience in a single institution. *J Thorac Cardiovasc Surg*. 2008;138:191–198.
16. Misthos P, Katsaragakis S, Kakaris S, et al. Descending necrotizing anterior mediastinitis: analysis of survival and surgical treatment modalities. *J Oral Maxillofac Surg*. 2007;65:635–639.
17. Gorjon PS, Perez PB, Martin ACM, et al. Deep neck infection: review of 286 cases. *Acta Otorrinolaringol Esp*. 2012;63:31–41.
18. Petitpas F, Blancal JP, Mateo J, et al. Factors associated with the mediastinal spread of cervical necrotizing fasciitis. *Ann Thorac Surg*. 2012;93:234–239.
19. Sarr MG, Gott VL, Townsend TR. Mediastinal infection after cardiac surgery. *Ann Thorac Surg*. 1984;38:415–423.
20. Loop FD, Lytle BW, Cosgrove DM, et al. Sternal wound complications after isolated coronary artery bypass grafting: early and late mortality, morbidity, and cost of care. *Ann Thorac Surg*. 1990;49:179–187.
21. Gummert JF, Barten MJ, Hans C, et al. Mediastinitis and cardiac surgery: an updated risk factor analysis in 10,373 consecutive patients. *Thorac Cardiovasc Surg*. 2002;50:87–91.
22. Hernandez F, Cohn WE, Baribeau YR, et al. In-hospital outcomes of off-pump versus on-pump coronary artery bypass procedures: a multicenter experience. *Ann Thorac Surg*. 2001;72:1528–1534.
23. Abboud CS, Wey SB, Balter VT. Risk factors for mediastinitis after cardiac surgery. *Ann Thorac Surg*. 2004;77:676–683.
24. Baillot R, Cloutier D, Montalin L, et al. Impact of deep sternal wound infection management with vacuum-assisted closure therapy followed by sternal osteosynthesis: a 15-year review of 23,499 sternotomies. *Eur J Cardiothorac Surg*. 2010;37:880–887.
25. Elenbaas TW, Soliman Hamad MA, Schonberger JP, et al. Preoperative atrial fibrillation and elevated C-reactive protein levels as predictors of mediastinitis after coronary artery bypass grafting. *Ann Thorac Surg*. 2010;89:704–709.
26. Risnes I, Abdelnoor M, Almdahl SM, et al. Mediastinitis after coronary artery bypass grafting risk factors and long-term survival. *Ann Thorac Surg*. 2010;89:1502–1510.
27. Berrios-Torres SI, Mu Y, Edwards JR, et al. Improved risk adjustment in public reporting: coronary artery bypass graft surgical site infections. *Infect Control Hosp Epidemiol*. 2012;33:463–469.
28. Fowler VG, O'Brien SM, Muhlbaier LH, et al. Clinical predictors of major infection after cardiac surgery. *Circulation*. 2005;30(suppl):I358–I365.
29. D'Agostino RS, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2018 update on outcomes and quality. *Ann Thorac Surg*. 2018;105:15–23.
30. Dandalides PC, Rutala WA, Sarubbi FA Jr. Postoperative infections following cardiac surgery: association with an environmental reservoir in a cardiothoracic intensive care unit. *Infect Control*. 1984;5:378–384.
31. Ehrenkranz NJ, Pfaff SJ. Mediastinitis complicating cardiac operations: evidence of postoperative causation. *Rev Infect Dis*. 1991;13:803–814.
32. Filsoufi F, Castillo JG, Rahmanian PB, et al. Epidemiology of deep sterna wound infection in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2009;23:488–494.
33. Kluytmans JA, Mouton JW, Ijzerman EP, et al. Nasal carriage of *Staphylococcus aureus* as a major risk factor for wound infection after cardiac surgery. *J Infect Dis*. 1995;171:216–219.
34. Robinson PJ, Billah B, Leder K, et al. Factors associated with deep sternal wound infection and haemorrhage following cardiac surgery in Victoria. *Interact Cardio Vasc Thorac Surg*. 2007;6:167–171.
35. Munoz P, Hortal J, Giannella M, et al. Nasal carriage of *S. aureus* increases the risk of surgical site infection after major heart surgery. *J Hosp Infect*. 2008;68:25–31.
36. Eklund AM, Lyytikainen O, Klemets P, et al. Mediastinitis after more than 10,000 cardiac surgical procedures. *Ann Thorac Surg*. 2006;82:1784–1789.
37. Perrault LP, Kirkwood KA, Chang HL, et al. A prospective multi-institutional cohort study of mediastinal infections after cardiac operations. *Ann Thorac Surg*. 2018;105:461–468.
38. Nieto-Cabrera M, Fernandez-Perez C, Garcia-Gonzalez I, et al. Med-Score 24: a multivariable prediction model for poststernotomy mediastinitis 24 hours after admission to the intensive care unit. *J Thorac Cardiovasc Surg*. 2018;155:1041–1051.
39. Lopez Gude MJ, San Juan R, Aguado JM, et al. Case-control study of risk factors for mediastinitis after cardiovascular surgery. *Infect Control Hosp Epidemiol*. 2006;27:1397–1400.
40. Molina JE, Lew RSL, Hyland KJ, et al. Postoperative sternal dehiscence in obese patients: incidence and prevention. *Ann Thorac Surg*. 2004;78:912–917.
41. Nishida H, Grooters RK, Soltanzadeh H, et al. Discriminate use of electrocautery on the median sternotomy incision. *J Thorac Cardiovasc Surg*. 1991;101:488–494.
42. Groom RC, Rassias AJ, Cormack JE, et al. Highest core temperature during cardiopulmonary bypass and rate of mediastinitis. *Perfusion*. 2004;19:119–125.
43. Hollenbeak CS, Murphy DM, Koenig S, et al. The clinical and economic impact of deep chest surgical site infections following coronary bypass graft surgery. *Chest*. 2000;118:397–402.
44. Przborowski J, Hartrumpf M, Stock UA, et al. Is bonewax safe and does it help? *Ann Thorac Surg*. 2008;85:1002–1006.
45. Cheng DC, Bainbridge D, Martin JE, et al. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *Anesthesiology*. 2005;102:188–203.
46. Stolinski J, Plicner D, Grudzien G, et al. A comparison of minimally invasive and standard aortic valve replacement. *J Thorac Cardiovasc Surg*. 2016;152:1030–1039.
47. Naage DL, Cale AR, Griffin S, et al. Is post-sternotomy percutaneous dilation tracheostomy a predictor for sternal wound infections? *Eur J Cardiothorac Surg*. 2008;33:1076–1081.
48. Pilarczyk K, Marggraf G, Dudasova M, et al. Tracheostomy after cardiac surgery with median sternotomy and risk of deep sternal wound infection: is it a matter of timing? *J Cardiothorac Vasc Anesthes*. 2015;29:1573–1581.
49. Lev-Ran O, Braunstein R, Nesher N, et al. Bilateral versus single internal thoracic artery grafting in oral-treated diabetic subsets: comparative seven-year outcome analysis. *Ann Thorac Surg*. 2004;77:2039–2045.
50. Danzer D, Christenson JT, Kalangos A, et al. Impact of double internal thoracic artery grafts on long-term outcomes in coronary artery bypass grafting. *Tex Heart Inst J*. 2001;28:89–95.
51. Arnold M. The surgical anatomy of sternal blood supply. *J Thorac Cardiovasc Surg*. 1972;64:596–610.
52. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, et al. The impact of deep sternal wound infection on long-term survival after coronary artery bypass grafting. *Chest*. 2005;127:464–471.
53. Toumpoulis IK, Theakos N, Dunning J. Does bilateral internal thoracic artery harvest increase the risk of mediastinitis? *Interact Cardiovasc Thorac Surg*. 2007;6:787–792.
54. Taggart DP, Altman DG, Gray AM, et al. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2016;375:2540–2549.
55. Momin AU, Deshpande R, Potts J, et al. Incidence of sternal infection in diabetic patients undergoing bilateral internal thoracic artery grafting. *Ann Thorac Surg*. 2005;80:1765–1772.
56. Iribarne A, Westbrook BM, Malenka DJ, et al. Should diabetes be a contraindication to bilateral internal mammary artery grafting? *Ann Thorac Surg*. 2018;105:709–714.
57. Ang LB, Veloria EN, Evanina EY, et al. Mediastinitis and blood transfusion in cardiac surgery: a systematic review. *Heart Lung*. 2012;41:255–263.
58. Chelemer SB, Prato S, Cox PM, et al. Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. *Ann Thorac Surg*. 2002;73:138–142.
59. Sreeram GM, Welsby IJ, Sharma AD, et al. Infectious complications after cardiac surgery: lack of association with fresh frozen plasma or platelet transfusions. *J Cardiothorac Vasc Anesth*. 2005;19:430–434.
60. Tiveron MG, Fiorelli AI, Mota EM, et al. Preoperative risk factors for mediastinitis after cardiac surgery: assessment of 2768 patients. *Rev Bras Cir Cardiovasc*. 2012;27:203–210.
61. Schmidt M, Brechot N, Hariri S, et al. Nosocomial infections in adult cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. *Clin Infect Dis*. 2012;55:1633–1641.
62. Baldwin RT, Radovancevic B, Sweeny MS, et al. Bacterial mediastinitis after heart transplantation. *J Heart Lung Transplant*. 1992;11:545–549.
63. Abid Q, Nkere UU, Hasan A, et al. Mediastinitis in heart and lung transplantation: 15 years' experience. *Ann Thorac Surg*. 2003;75:1565–1571.
64. Senechal M, LePrince P, du Montcel ST, et al. Bacterial mediastinitis after heart transplant: clinical presentation, risk factors, and treatment. *J Heart Lung Transplant*. 2004;23:165–170.
65. Filsoufi F, Rahmanian PB, Castillo JG, et al. Incidence, treatment strategies and outcome of deep sternal wound infection after orthotopic heart transplantation. *J Heart Lung Transplant*. 2007;26:1084–1090.
66. Zuckermann A, Arizon JM, Dong G, et al. Impact of de novo everolimus-based immunosuppression on incisional complications in heart transplantation. *Transplantation*. 2011;92:594–600.
67. Kuppahally S, Al-Khaldi A, Weisshaar D, et al. Wound healing complications with de novo sirolimus versus mycophenolate mofetil-based regimen in cardiac transplant recipients. *Am J Transplant*. 2006;6:986–992.
68. Monkowski DH, Axelrod P, Fekete T, et al. Infections associated with ventricular assist devices: epidemiology and effect on prognosis after transplantation. *Transpl Infect Dis*. 2007;9:114–120.
69. Burket JS, Chenoweth CE, Meyer TL, et al. Donor-to recipient transmission of bacteria as an unusual cause of mediastinitis. *Infect Control Hosp Epidemiol*. 1999;20:132–133.
70. Al-Sehly AA, Robinson JL, Lee BE, et al. Pediatric poststernotomy mediastinitis. *Ann Thorac Surg*. 2005;80:2314–2320.
71. Barker GM, O'Brien SM, Welke KF, et al. Major infection after pediatric cardiac surgery: a risk estimation model. *Ann Thorac Surg*. 2010;89:843–850.
72. Kansy A, Jacobs JP, Pastuszko A, et al. Major infection after pediatric cardiac surgery: external validation of risk estimation model. *Ann Thorac Surg*. 2012;94:2091–2096.
73. Sohn AH, Schwartz JM, Yang KY, et al. Risk factors and risk adjustment for surgical site infections in pediatric cardiothoracic surgery patients. *Am J Infect Control*. 2010;38:706–710.
74. Costello JM, Graham DA, Forbes Morrow D, et al. Risk factors for surgical site infection after cardiac surgery in children. *Ann Thorac Surg*. 2010;89:1833–1842.
75. Kagan J, Lautenbach E, Bilker WB, et al. Risk factors for mediastinitis following median sternotomy in children. *Pediatr Infect Dis J*. 2007;26:613–618.
76. Ozker E, Saritas B, Vuran C, et al. Delayed sternal closure after pediatric cardiac operations; single center experience: a retrospective study. *J Cardiothorac Surg*. 2012;7:102.
77. Long CB, Shah SS, Lautenbach E, et al. Postoperative mediastinitis in children: epidemiology, microbiology, and risk factors for gram-negative pathogens. *Pediatr Infect Dis J*. 2005;24:315–319.

78. Wang JT, Chang SC, Ko WJ, et al. A hospital-acquired outbreak of methicillin-resistant *Staphylococcus aureus* infection initiated by a surgeon carrier. *J Hosp Infect*. 2001;47:104–109.
79. Weinstein HJ. The relationship between the nasal-staphylococcal-carrier state and the incidence of postoperative complications. *N Engl J Med*. 1959;260:1303–1310.
80. Archer GL, Armstrong BC. Alteration of staphylococcal flora in cardiac surgery patients receiving antibiotic prophylaxis. *J Infect Dis*. 1983;147:642–649.
81. Olsson E, Friberg O, Venizelos N, et al. Coagulase-negative staphylococci isolated from sternal wound infections after cardiac surgery: attachment to and accumulation on sternal fixation stainless steel wires. *APMIS*. 2007;115:142–151.
82. Ashley ESD, Carroll DN, Engemann JJ, et al. Risk factors for postoperative mediastinitis due to methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2004;38:1555–1560.
83. San Juan R, Chaves F, Lopez Gude MJ, et al. Staphylococcus aureus poststernotomy mediastinitis: description of two distinct acquisition pathways with different potential preventive approaches. *J Thorac Cardiovasc Surg*. 2007;134:670–671.
84. Kirklin JK, Westaby S, Blackstone EH, et al. Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1983;86:845–857.
85. Andersen BM, Sorlie D, Hotvedt R, et al. Multiply beta-lactam resistant *Enterobacter cloacae* infections linked to the environmental flora in a unit for cardiothoracic and vascular surgery. *Scand J Infect Dis*. 1989;21:181–191.
86. Palaez T, Munuz P, Guinea J, et al. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the intensive care unit. *Clin Infect Dis*. 2012;54:e24–e31.
87. Sax H, Bloemberg G, Hasse B, et al. Prolonged outbreak of *Mycobacterium chimaera* infection after open-chest heart surgery. *Clin Infect Dis*. 2015;61:67–75.
88. Trouillet JL, Vuagnat A, Combes A, et al. Acute poststernotomy mediastinitis managed with debridement and closed-drainage aspiration: factors associated with death in the intensive care unit. *J Thorac Cardiovasc Surg*. 2005;129:518–524.
89. Mekontso Dessap AM, Vivier E, Girou E, et al. Effect of time to onset on clinical features and prognosis of post-sternotomy mediastinitis. *Clin Microbiol Infect*. 2011;17:292–299.
90. Tammelin A, Hambraeus A, Stahle E. Mediastinitis after cardiac surgery: improvement of bacteriological diagnosis by use of multiple tissue samples and strain typing. *J Clin Microbiol*. 2002;40:2936–2941.
91. Gardlund B, Bitkover CY, Vaage J. Postoperative mediastinitis in cardiac surgery—microbiology and pathogenesis. *Eur J Cardiothorac Surg*. 2002;21:825–830.
92. Clancy CJ, Nguyen MH, Morris AJ. Candidal mediastinitis: an emerging clinical entity. *Clin Infect Dis*. 1997;25:608–613.
93. Modrau IS, Ejlertsen T, Rasmussen BS. Emerging role of *Candida* in deep sternal wound infection. *Ann Thorac Surg*. 2009;88:1905–1909.
94. Murray M, Finegold SM. Anaerobic mediastinitis. *Rev Infect Dis*. 1984;6:S123–S127.
95. Hamman L. Spontaneous mediastinal emphysema. *Bull Johns Hopkins Hosp*. 1939;64:1–21.
96. Feldman R, Gromisch DS. Acute suppurative mediastinitis. *Am J Dis Child*. 1971;121:79–81.
97. Abdullah AA, Robinson JL, Lee BE, et al. Pediatric poststernotomy mediastinitis. *Ann Thorac Surg*. 2005;80:2314–2320.
98. Corsten MJ, Shamji FM, Odell PF, et al. Optimal treatment of descending necrotizing mediastinitis. *Thorax*. 1997;52:702–708.
99. Weaver E, Nguyen X, Brooks MA. Descending necrotizing mediastinitis: two case reports and review of the literature. *Eur Respir Rev*. 2010;19:141–149.
100. Fritscher-Ravens A, Schirrow L, Pothmann W, et al. Critical care transesophageal endosonography and guided fine-needle aspiration for diagnosis and management of posterior mediastinitis. *Crit Care Med*. 2003;31:126–132.
101. Kao CH, Wang SJ. Spread of infectious complications of odontogenic abscess detected by technetium-99m-HMPAO-labeled WBC scan of occult sepsis in the intensive care unit. *J Nucl Med*. 1992;33:254–255.
102. Han SY, McElvein RB, Aldrete JS, et al. Perforation of the esophagus: correlation of site and cause with plain film findings. *AJR Am J Roentgenol*. 1985;145:537–540.
103. Keeling WB, Miller DL, Lam GT, et al. Low mortality after treatment for esophageal perforation: a single-center experience. *Ann Thorac Surg*. 2010;90:1669–1673.
104. Schweigert M, Sousa HS, Solymosi N, et al. Spotlight on esophageal perforation: a multinational study using the Pittsburgh esophageal perforation severity scoring system. *J Thorac Cardiovasc Surg*. 2016;151:1002–1011.
105. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002. *JAMA*. 2002;287:2236–2252.
106. Karra R, McDermott L, Connelly S, et al. Risk factors for 1-year mortality after postoperative mediastinitis. *J Thorac Cardiovasc Surg*. 2006;132:537–543.
107. Simpson LC, Peters GE. Poststernotomy infections presenting as deep neck abscess. *Arch Otolaryngol Head Neck Surg*. 1988;114:909–912.
108. Sponholz C, Sakr Y, Reinhart K, et al. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. *Crit Care*. 2006;10:R145–R156.
109. Hammer S, Meisner F, Dirschedl P, et al. Procalcitonin for differential diagnosis of graft rejection and infection in patients with heart and/or lung grafts. *Intensive Care Med*. 2000;26:S182–S186.
110. San Juan R, Aguado JM, Lopez MJ, et al. Accuracy of blood culture for early diagnosis of mediastinitis in febrile patients after cardiac surgery. *Eur J Clin Microbiol Infect Dis*. 2005;24:182–189.
111. Akman C, Kantarci F, Cetinkaya S. Imaging in mediastinitis: a systematic review based on aetiology. *Clin Radiol*. 2004;59:573–585.
112. Gur E, Stern D, Weiss J, et al. Clinical-radiological evaluation of poststernotomy wound infection. *Plast Reconstr Surg*. 1998;101:348–355.
113. Quirce R, Serano J, Arnal C, et al. Detection of mediastinitis after heart transplantation by gallium-67 scintigraphy. *J Nucl Med*. 1991;32:860–861.
114. Bitkover CY, Garlund B, Larsson SA, et al. Diagnosing sternal wound infections with 99mTc-labeled monoclonal granulocyte antibody scintigraphy. *Ann Thorac Surg*. 1996;62:1412–1417.
115. Browdie DA, Bernstein RW, Agnew R, et al. Diagnosis of post-sternotomy infection: comparison of three means of assessment. *Ann Thorac Surg*. 1991;51:290–292.
116. Maroto LC, Aguado JM, Carrascal Y, et al. Role of epicardial pacing wire cultures in the diagnosis of poststernotomy mediastinitis. *Clin Infect Dis*. 1997;24:419–421.
117. Mekontso-Dessap A, Honore S, Kirsch M, et al. Usefulness of routine epicardial pacing wire culture for early prediction of poststernotomy mediastinitis. *J Clin Microbiol*. 2004;42:5245–5248.
118. Benlolo S, Mateo J, Raskine L, et al. Sternal puncture allows an early diagnosis of poststernotomy mediastinitis. *J Thorac Cardiovasc Surg*. 2003;125:611–617.
119. Barrett NR. Report of a case of spontaneous perforation of the oesophagus successfully treated by operation. *Br J Surg*. 1947;35:216–218.
120. Jougon J, McBride T, Delcambre F, et al. Primary esophageal repair for Boerhaave's syndrome whatever the free interval between perforation and treatment. *Eur J Cardiothorac Surg*. 2004;25:475–479.
121. Abbas G, Schuchert MJ, Pettiford BL, et al. Contemporaneous management of esophageal perforation. *Surgery*. 2009;146:749–756.
122. Lindenmann J, Matzi V, Neuboeck N, et al. Management of esophageal perforation in 120 consecutive patients: clinical impact of a structured treatment algorithm. *J Gastointest Surg*. 2013;17:1036–1043.
123. Kirschniak A, Subotova N, Zieker D, et al. The over-the-scope clip (OTSC) for the treatment of gastrointestinal bleeding, perforations, and fistulas. *Surg Endosc*. 2011;25:2901–2905.
124. Qadeer MA, Dumot JA, Vargo JJ, et al. Endoscopic clips for closing esophageal perforations: case report and pooled analysis. *Gastrointest Endosc*. 2007;66:605–611.
125. Thornblade LW, Cheng AM, Wood DE, et al. A nationwide rise in the use of stents for benign esophageal perforation. *Ann Throac Surg*. 2017;104:227–233.
126. van Boeckel PGA, Sijbring A, Vleggaar FP, et al. Systematic review: temporary stent placement for benign rupture or anastomotic leak of the oesophagus. *Aliment Pharmacol Ther*. 2011;33:1292–1301.
127. Freeman RK, Herrera A, Ascioti AJ, et al. A propensity-matched comparison of cost and outcomes after esophageal stent placement or primary surgical repair for iatrongenic esophageal perforation. *J Thorac Cardiovasc Surg*. 2015;149:1550–1555.
128. Martinez L, Rivas S, Hernandez F, et al. Aggressive conservative treatment of esophageal perforations in children. *J Pediatr Surg*. 2003;38:685–689.
129. Demirbag S, Tiryaki T, Atabek C, et al. Conservative approach to the mediastinitis in childhood secondary to esophageal perforation. *Clin Pediatr*. 2005;44:131–134.
130. Mora R, Jankowska B, Catrambone U, et al. Descending necrotizing mediastinitis: ten years' experience. *Ear Nose Throat J*. 2004;83:774–780.
131. Hsu RF, Wu PY, Ho CK. Transcervical drainage for descending necrotizing mediastinitis may be sufficient. *Otolaryngol Head Neck Surg*. 2011;142:742–747.
132. Ridder GJ, Maier W, Kinzer S, et al. Descending necrotizing mediastinitis: contemporary trends in etiology, diagnosis, management, and outcome. *Ann Surg*. 2010;251:528–534.
133. Palma DM, Giuliano S, Cracchiolo AN, et al. Clinical features and outcome of patients with descending necrotizing mediastinitis: prospective analysis of 34 cases. *Infection*. 2016;44:77–84.
134. Min HK, Choi YS, Shim YM, et al. Descending necrotizing mediastinitis: a minimally invasive approach using video-assisted thoracoscopic surgery. *Ann Thorac Surg*. 2004;77:306–310.
135. Sumi Y, Ogura H, Nakamori Y, et al. Nonoperative catheter management for cervical necrotizing fasciitis with and without descending necrotizing mediastinitis. *Arch Otolaryngol Head Neck Surg*. 2008;134:750–756.
136. Gobien RP, Stanley JH, Gobien BS, et al. Percutaneous catheter aspiration and drainage of suspected mediastinal abscesses. *Radiology*. 1984;151:69–71.
137. Song DH, Wu LC, Lohman RF, et al. Vacuum assisted closure for the treatment of sternal wounds: the bridge between debridement and definitive closure. *Plast Reconstr Surg*. 2003;3:92–97.
138. Agarwal JP, Ogilvie M, Wu LC, et al. Vacuum-assisted closure for sternal wounds: a first-line therapeutic management approach. *Plast Reconstr Surg*. 2005;116:1035–1040.
139. Sjogren J, Gustafsson R, Nilsson J, et al. Clinical outcome after poststernotomy mediastinitis: vacuum-assisted closure versus conventional treatment. *Ann Thorac Surg*. 2005;79:2049–2055.
140. Petzina R, Hoffman J, Navasardyan A, et al. Negative pressure therapy for post-sternotomy mediastinitis reduces mortality rate and sternal re-infection rate compared to conventional treatment. *Eur J Cardiothorac Surg*. 2010;38:110–113.
141. Falagas ME, Tansarli G, Kapaskelis A, et al. Impact of vacuum-assisted closure (VAC) therapy on clinical outcomes of patients with sternal wound infections: a meta-analysis of non-randomized studies. *PLoS ONE*. 2013;8:e64741.
142. Raja S, Berg GA. Should vacuum-assisted closure therapy be routinely used for management of deep sternal wound infection after cardiac surgery? *Interact Cardiovasc Thorac Surg*. 2007;6:523–528.
143. Molina JE, Nelson EC, Smith RA. Treatment of postoperative sternal dehiscence with mediastinitis: twenty-four-year use of a single method. *J Thorac Cardiovasc Surg*. 2006;132:782–787.
144. Merrill WH, Akhter SA, Wolf RK, et al. Simplified treatment of postoperative mediastinitis. *Ann Thorac Surg*. 2004;78:608–612.
145. Lazar HL, Salm TV, Englelman R, et al. Prevention and management of sternal wound infections. *J Thorac Cardiovasc Surg*. 2016;152:962–972.
146. Jones G, Jurkiewicz MJ, Bostwick J, et al. Management of the infected median sternotomy wound with muscle flaps. *Ann Surg*. 1997;225:766–778.
147. Nahai F, Rand RP, Hester TR, et al. Primary treatment of the infected sternotomy wound with muscle flaps: a review of 211 consecutive cases. *Plast Reconstr Surg*. 1989;84:434–441.
148. Eifert S, Kronschnabl S, Kaczmarek I, et al. Omental flap for recurrent deep sternal wound infection and mediastinitis after cardiac surgery. *Thorac Cardiovasc Surg*. 2007;55:371–374.
149. Jacobs B, Ghersi MM. Intercostal artery-based rectus abdominis transposition flap for sternal wound reconstruction. *Ann Plast Surg*. 2008;60:410–415.
150. Wong CH, Senewiratne S, Garlick B, et al. Two-stage management of sternal wound infection using bilateral pectoralis major advancement flap. *Eur J Cardiothorac Surg*. 2006;30:148–152.
151. Chiang IH, Chen SG, Wang CH. Treatment of sternal wound infection using a free myocutaneous flap. *Ann Thorac Surg*. 2015;100:1907–1910.
152. Fleck TM, Koller R, Giovanoli P, et al. Primary or delayed closure for the treatment of poststernotomy wound infections. *Ann Plastic Surg*. 2004;52:310–314.
153. Kopel ME, Riemersma L, Finlayson DC, et al. Gentamicin solution for mediastinal irrigation: systemic absorption, bactericidal activity, and toxicity. *Ann Thorac Surg*. 1989;48:228–231.
154. Kratz JM, Metcalf JS, Sade RM. Pericardial injury by antibacterial irrigants. *J Thorac Cardiovasc Surg*. 1983;86:785–787.
155. Glick PL, Guglielmo BJ, Tranbaugh RF, et al. Iodine toxicity in a patient treated by continuous povidone-iodine mediastinal irrigation. *Ann Thorac Surg*. 1985;39:478–480.

156. Engemann JJ, Carmeli Y, Cosgrove SE, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. *Clin Infect Dis*. 2003;36:592–598.
157. Mekontso-Dessap A, Kirsch M, Brun-Buisson C, et al. Poststernotomy mediastinitis due to *Staphylococcus aureus:* comparison of methicillin-resistant and methicillin-susceptible cases. *Clin Infect Dis*. 2001;32:877–883.
158. Combes A, Trouillet JL, Joly-Guillou ML, et al. The impact of methicillin resistance on the outcome of poststernotomy mediastinitis due to *Staphylococcus aureus*. *Clin Infect Dis*. 2004;38:822–829.
159. Reddy SLC, Grayson AD, Smith G, et al. Methicillin resistant *Staphylococcus aureus* infections following cardiac surgery: incidence, impact, and identifying adverse outcome traits. *Eur J Cardiothorac Surg*. 2007;32:113–117.
160. Efem SE. Clinical observations on the wound healing properties of honey. *Br J Surg*. 1988;75:679–681.
161. DeFeo M, De Santo LS, Romano G, et al. Treatment of recurrent staphylococcal mediastinitis: still a controversial issue. *Ann Thorac Surg*. 2003;75:538–542.
162. Jull AB, Walker N, Deshpande S. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev*. 2013;(2):CD005083.
163. De Feo M, Della Corte A, Vicchio M, et al. Is post-sternotomy mediastinitis still devastating after the advent of negative-pressure wound therapy? *Tex Heart Inst J*. 2011;38:375–380.
164. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70:195–283.
165. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2011;58:e123–e210.
166. Rebmann T, Kohut K. Preventing mediastinitis surgical site infections: executive summary of the association for professionals in infection control and epidemiology elimination guide. *Am J Infect Control*. 2011;39:529–531.
167. Kramer R, Groom R, Weldner D, et al. Glycemic control and reduction of deep sternal wound infection rates. *Arch Surg*. 2008;143:451–456.
168. Carr JM, Sellke FW, Fey M, et al. Implementing tight glucose control after coronary artery bypass surgery. *Ann Thorac Surg*. 2005;80:902–909.
169. Furnary AP, Zerr KJ, Grunkemeier GL, et al. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg*. 1999;67:352–362.
170. Edwards FH, Engelman RM, Houck P, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part I: duration. *Ann Thorac Surg*. 2006;81:397–404.
171. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part II: antibiotic choice. *Ann Thorac Surg*. 2007;93:1569–1576.
172. Abramowicz M. Antimicrobial prophylaxis in surgery. *Med Lett*. 2001;43:92–98.
173. Maki DG, Bohn MJ, Stolz SM, et al. Comparative study of cefazolin, cefamandole, and vancomycin for surgical prophylaxis in cardiac and vascular operations. *J Thorac Cardiovasc Surg*. 1992;104:1423–1434.
174. Chambers D, Worthy G, Myers L, et al. Glycopeptide vs. non-glycopeptide antibiotics for prophylaxis of surgical site infections: a systematic review. *Surg Infect (Larchmt)*. 2010;11:455–462.
175. Lador A, Nasir H, Mansur N, et al. Antibiotic prophylaxis in cardiac surgery: systematic review and meta-analysis. *J Antimicrob Chemother*. 2012;67:541–550.
176. Bolon MK, Morlote M, Weber SG, et al. Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. *Clin Infect Dis*. 2004;38:1357–1363.
177. Harbarth S, Samore MH, Lichtenberg D, et al. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation*. 2000;101:2916–2921.
178. Mertz D, Johnstone J, Loeb M. Does duration of perioperative antibiotic prophylaxis matter in cardiac surgery? A systematic review and meta-analysis. *Ann Surg*. 2011;254:48–54.
179. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA*. 2017;152:784–791.
180. Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol*. 2005;26:916–922.
181. Shrestha NK, Banbury MK, Weber M, et al. Safety of targeted perioperative mupirocin treatment for preventing infections after cardiac surgery. *Ann Thorac Surg*. 2006;81:2183–2188.
182. Bode LG, Kluytmans AJ, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med*. 2010;362:9–17.
183. Fowler VG, Allen KB, Moreira ED, et al. Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery: a randomized trial. *JAMA*. 2013;309:1368–1378.
184. Vander Salm TJ, Okike ON, Pasque MK, et al. Reduction of sternal infection by application of topical vancomycin. *J Thorac Cardiovasc Surg*. 1989;98:618–622.
185. Lazar HL, Ketchedjian A, Haime M, et al. Topical vancomycin in combination with perioperative antibiotics and tight glycemic control helps to eliminate sternal wound infections. *J Thorac Cardiovasc Surg*. 2014;148:1035–1040.
186. Lander HL, Ejiofor JI, McGurk S, et al. Vancomycin paste doe not reduce the incidence of deep sternal wound infection after cardiac operations. *Ann Thorac Surg*. 2017;103:497–503.
187. Kowalewski M, Faffa GM, Szwed KA, et al. Meta-analysis to assess the effectiveness of topically used vancomycin in reducing sternal wound infections after cardiac surgery. *J Thorac Cardiovasc Surg*. 2017;154:1320–1323.
188. Eklund AM, Valtonen M, Werkkala KA. Prophylaxis of sternal wound infections with gentamicin-collagen implant: randomized controlled study in cardiac surgery. *J Hosp Infect*. 2005;59:108–112.
189. Friberg O, Svedjeholm R, Soderquist B, et al. Local gentamicin reduces sternal wound infections after cardiac surgery: a randomized controlled trial. *Ann Thorac Surg*. 2005;79:153–162.
190. Bennett-Guerrero E, Ferguson TB, Lin M, et al. Effect of an implantable gentamicin-collagen sponge on sternal wound infections following cardiac surgery: a randomized trial. *JAMA*. 2010;304:755–762.
191. Schimmer C, Ozkur M, Sinha B, et al. Gentamicin-collagen sponge reduces wound complications after heart surgery: a controlled, prospectively randomized double-blind study. *J Thorac Cardiovasc Surg*. 2012;143:194–200.
192. Mavros MN, Mitsikostas PK, Alexiou VG, et al. Gentamicin collagen sponges for the prevention of sternal wound infection: a meta-analysis of randomized controlled trials. *J Thorac Cardiovasc Surg*. 2012;144:1235–1240.
193. Kowalewski M, Pawliszak W, Zaborowska K, et al. Gentamicin-collagen sponge reduces the risk of sternal wound infections after heart surgery: meta-analysis. *J Thorac Cardiovasc Surg*. 2015;149:1631–1640, e6.
194. Gatti G, Ledwon M, Gazdag L, et al. Management of closed sternal incision after bilateral internal thoracic artery grafting with a single-use negative pressure system. *Updates Surg*. 2018;70:545–552.
195. Grauhan O, Navasardyan A, Hofmann M, et al. Prevention of poststernotomy wound infections in obese patients by negative pressure wound therapy. *J Thorac Cardiovasc Surg*. 2013;145:1387–1392.
196. Markar SR, Mackenzie H, Wiggins T, et al. Management and outcomes of esophageal perforations: a national study of 2,264 patients in England. *Am J Gastoenterol*. 2015;110:1559–1566.
197. Biancari F, D'Andrea V, Paone R, et al. Current treatment and outcome of esophageal perforations in adults: systematic review and meta-analysis of 75 studies. *World J Surg*. 2013;37:1051–1059.
198. Sudarshan M, Elharram M, Spicer J, et al. Management of esophageal perforation in the endoscopic era: is operative repair still relevant? *Surgery*. 2016;160:1104–1110.
199. Kocher GJ, Hoksch B, Caversaccio M, et al. Diffuse descending necrotizing mediastinitis: surgical therapy and outcome in a single-centre series. *Eur J Cardiothorac Surg*. 2012;42:e66–e72.
200. Immer FF, Durrer M, Muhlemann KS, et al. Deep sternal wound infection after cardiac surgery: modality of treatment and outcome. *Ann Thorac Surg*. 2005;80:957–961.
201. Cayci C, Russo M, Cheema F, et al. Risk analysis of deep sternal wound infections and their impact on long-term survival: a propensity analysis. *Ann Plast Surg*. 2008;61:294–301.
202. Domart Y, Trouillet JL, Fagon JY, et al. Incidence and morbidity of cytomegaloviral infection in patients with mediastinitis following cardiac surgery. *Chest*. 1990;97:18–22.
203. Morisaki A, Hosono M, Sasaki Y, et al. Evaluation of risk factors for hospital mortality and current treatment for poststernotomy mediastinitis. *Gen Thorac Cardiovasc Surg*. 2011;59:261–267.
204. Graf K, Ott E, Vonberg RP, et al. Economic aspects of deep sternal wound infections. *Eur J Cardiothorac Surg*. 2010;37:893–896.
205. Calderwood MS, Kleinman K, Soumerai SB, et al. Impact of Medicare's payment policy on mediastinitis following coronary artery bypass graft surgery in US hospitals. *Infect Control Hosp Epidemiol*. 2014;35:144–151.
206. Schowengerdt CG, Suyemoto R, Main FB. Granulomatous and fibrous mediastinitis. *J Thorac Cardiovasc Surg*. 1969;57:365–379.
207. Hache L, Woolner LB, Bernatz PE. Idiopathic fibrous mediastinitis. *Dis Chest*. 1962;41:9–25.
208. Gryboski WA, Crutcher RR, Holloway JB, et al. Surgical aspects of histoplasmosis. *Arch Surg*. 1963;87:590–599.
209. Peabody JW, Brown RB, Sullivan MB, et al. Mediastinal granulomas. *J Thorac Surg*. 1958;35:384–396.
210. Peikert T, Colby TV, Midthun DE, et al. Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response. *Medicine (Baltimore)*. 2011;90:412–423.
211. Ramakantan R, Shah P. Dysphagia due to mediastinal fibrosis in advanced pulmonary tuberculosis. *AJR Am J Roentgenol*. 1990;154:61–63.
212. Bennhoff DF. Actinomycosis: diagnostic and therapeutic considerations and a review of 32 cases. *Laryngoscope*. 1984;94:1198–1217.
213. Poland GA, Jorgensen CR, Sarosi GA. *Nocardia asteroides* pericarditis: report of a case and review of the literature. *Mayo Clin Proc*. 1990;65:819–824.
214. Ahmad M, Weinstein AJ, Hughes JA, et al. Granulomatous mediastinitis due to *Aspergillus flavus* in a nonimmunocompromised patient. *Am J Med*. 1981;70:887–890.
215. Leong AS. Granulomatous mediastinitis due to *Rhizopus* species. *Am J Clin Pathol*. 1978;70:103–107.
216. Robertson BD, Bautista MA, Russell TS, et al. Fibrosing mediastinitis secondary to zygomycosis in a twenty-two month old child. *Pediatr Infect Dis*. 2002;21:441–442.
217. Gilbert HM, Hartman BJ. Short report: a case of fibrosing mediastinitis caused by Wuchereria bancrofti. *Am J Trop Med Hyg*. 1996;54:596–599.
218. Case records of the Massachusetts General Hospital (case 6–1989). *N Engl J Med*. 1989;320:380–389.
219. Grotty TB, Colby TV, Gay PC, et al. Desmoplastic malignant mesothelioma masquerading as sclerosing mediastinitis. *Hum Pathol*. 1992;23:79–82.
220. Kanne JP, Mohammed T. Fibrosing mediastinitis associated with Behçet's disease: CT findings. *Clin Radiol*. 2007;62:1124–1126.
221. Flieder DB, Suster S, Moran CA. Idiopathic fibroinflammatory (fibrosing/sclerosing) lesions of the mediastinum: a study of 30 cases with emphasis on morphological heterogeneity. *Mod Pathol*. 1999;12:257–264.
222. Afrin LB. Sclerosing mediastinitis and mast cell activation syndrome. *Pathol Res Pract*. 2012;208:181–185.
223. Peikert T, Shrestha B, Aubry MC, et al. Histopathologic overlap between fibrosing mediastinitis and IgG4-related disease. *Int J Rheumatol*. 2012;2012:207056.
224. Sakamoto A, Nagai R, Saito K, et al. Idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pericarditis—retrospective analysis of 11 case histories. *J Cardiol*. 2012;59:139–146.
225. Loeb JM, Lombard CM. Idiopathic mediastinitis with superior vena cava obstruction, cardiac tamponade, and cutaneous vasculitis. *West J Med*. 1991;155:296–299.
226. Williamson WA, Tronic BS, Levitan N, et al. Pulmonary venous infarction. *Chest*. 1992;102:937–940.
227. Sherrick AD, Brown LR, Harms GF, et al. The radiographic findings of fibrosing mediastinitis. *Chest*. 1994;106:484–489.
228. Rossi SE, McAdams P, Rosado-de-Christenson ML, et al. Fibrosing mediastinitis. *Radiographics*. 2001;21:737–757.
229. Rholl KS, Levitt RG, Glaser HS. Magnetic resonance imaging of fibrosing mediastinitis. *Am J Roentgenol*. 1985;145:255–259.
230. McNeely MF, Chung JH, Bhalla S, et al. Imaging of granulomatous fibrosing mediastinitis. *Am J Roentgenol*. 2012;199:319–327.
231. Strock SB, Gaudieri S, Mallal S, et al. Fibrosing mediastinitis complicating prior histoplasmosis is associated with human leukocyte antigen DQB1*04:02—a case control study. *BMC Infect Dis*. 2015;15:206.
232. Urschel HC Jr, Razzuk MA, Netto GJ, et al. Sclerosing mediastinitis: improved management with histoplasmosis titer and ketoconazole. *Ann Thorac Surg*. 1990;50:215–221.
233. Seferian A, Steriade A, Jais X, et al. Pulmonary hypertension complicating fibrosing mediastinitis. *Medicine (Baltimore)*. 2015;94:e1800.

234. van Bommel EFH, Hendriksz TR, Huiskes AW, et al. Brief communication: tamoxifen therapy for nonmalignant retroperitoneal fibrosis. *Ann Intern Med*. 2006;144:101–106.
235. Savelli BA, Parshley M, Morganroth ML. Successful treatment of sclerosing cervicitis and fibrosing mediastinitis with tamoxifen. *Chest*. 1997;111:1137–1140.
236. Zajtchuk R, Strevey TE, Heydorn WH, et al. Mediastinal histoplasmosis: surgical considerations. *J Thorac Cardiovasc Surg*. 1973;66:300–304.
237. Albers EL, Pugh ME, Hill KD, et al. Percutaneous stent implantation as treatment for central vascular obstruction due to fibrosing mediastinitis. *Circulation*. 2011;123:1391–1399.
238. Ponamgi SP, DeSimone CV, Lenz CJ, et al. Catheter-based intervention for pulmonary vein stenosis due to fibrosing mediastinitis: the Mayo Clinic experience. *Int J Cardiol Heart Vasc*. 2015;8:103–107.

H Central Nervous System Infections

86 Approach to the Patient With Central Nervous System Infection

Rodrigo Hasbun and Allan R. Tunkel

The central nervous system (CNS) may be infected by various agents, including viruses, bacteria, fungi, protozoa, and helminthes. In addition, numerous noninfectious etiologies may account for syndromes that mimic CNS infections. These include neoplastic diseases, intracranial tumors and cysts, medications, collagen vascular disorders, autoimmune disorders and other systemic illnesses, and conditions arising after various procedures that invade the CNS. The clinical presentation of a CNS infection may be acute, subacute, or chronic, depending on the virulence of the infecting agent and the location of the infection. Because CNS infections occur within the confines of the cranium or spinal column, they may be associated with significant morbidity and mortality, often necessitating emergent administration of antimicrobial therapy, and even neurosurgical interventions, to improve outcome. This chapter reviews the general approach to infections of the CNS, which are discussed in further detail in subsequent chapters of this section.

CLINICAL MANIFESTATIONS

The clinical presentation of a specific CNS infection depends on the pathogenesis of spread of the infection to the CNS, the virulence of the etiologic agent, and the area of CNS involvement. Most patients with CNS infections present with the clinical manifestations of fever, headache, altered mental status, or focal neurologic deficits. These findings are nonspecific, however, and not all patients with CNS infections develop all of these clinical manifestations. The likelihood of any specific clinical finding depends on the CNS syndrome caused by the infectious agent. These are reviewed subsequently.

Meningitis

Patients with acute meningitis most often present with fever, headache, meningismus, and altered mental status (see Chapter 87).[1,2] A typical adult patient with acute bacterial meningitis usually seeks medical attention within a few hours to several days after the onset of illness. The presentation may vary, depending on the age of the patient and the presence of various underlying conditions, for instance, head trauma, recent neurosurgery, presence of a cerebrospinal fluid (CSF) shunt (see Chapter 92), and immunocompromised state. The presentation may also vary depending on the microorganism causing meningitis. The most common etiologic agents of acute meningitis are unknown. When a cause is identified, viruses (most often enteroviruses; children > adults), West Nile virus (WNV), and herpes simplex virus (HSV) type 2 (adults), but also human immunodeficiency virus (HIV), varicella-zoster virus (VZV), less likely mumps virus, and bacteria (e.g., *Streptococcus pneumoniae, Neisseria meningitidis*, and *Listeria monocytogenes*).[2] Less commonly, parasites (e.g., *Naegleria fowleri* and *Angiostrongylus cantonensis)* may cause acute meningitis.

In contrast, patients with subacute (>5 days but <30 days of symptoms) or chronic meningitis (>30 days of symptoms) typically present over weeks to months, or even years (see Chapter 88).[1,2] These patients are more likely to be immunosuppressed, have abnormal neurologic findings, and to have hypoglycorrhachia with less pronounced CSF pleocytosis.[2] The most common etiology is idiopathic, but tuberculous meningitis and fungal meningitis (e.g., caused by *Cryptococcus neoformans, Histoplasma* spp., and *Coccidioides* spp.) are important considerations.[1,2] The clinical presentation of cryptococcal meningitis is different in patients with and without acquired immunodeficiency syndrome (AIDS). In non-AIDS patients cryptococcal meningitis is typically a subacute process, in which patients have days to weeks of symptoms characterized by headache, fever, meningismus, and personality changes. In AIDS patients the presentation is subtler with minimal, if any, symptoms; these patients may present with only headache and lethargy, with meningeal findings seen in only a few cases. Other fungi, such as *Candida* and *Aspergillus*, are unusual causes of meningitis, although cases of *Exserohilum rostratum* meningitis were reported in association with epidural or paraspinal glucocorticoid injections of preservative-free methylprednisolone from a single compounding pharmacy.[3]

Encephalitis

The syndrome of acute encephalitis is manifested by parenchymal brain inflammation that causes neurologic dysfunction (see Chapter 89).[4,5] An international consortium recently defined encephalitis with a combination of major and minor criteria. The major criteria are altered mental status (defined as a decreased, altered level of consciousness, lethargy, or personality change) lasting ≥24 hours without an alternative diagnosis and is a requirement for the diagnosis. The six minor criteria are (1) documented fever ≥38°C (100.4°F) within 72 hours before or after presentation, (2) seizures not attributable to a preexisting seizure disorder, (3) new-onset focal neurologic findings, (4) CSF white blood cells (WBCs) ≥5/mm^3, (5) new- or acute-onset neuroimaging abnormalities consistent with encephalitis, and (6) abnormalities on electroencephalography consistent with encephalitis and not secondary to other etiologies. The presence of two minor criteria indicate possible encephalitis, and greater than or equal to three indicate probable or confirmed encephalitis, if the etiologic agent is confirmed by brain biopsy, serologies, polymerase chain reaction (PCR), or antibodies in patients with autoimmune encephalitis. A clinical overlap between encephalitis and encephalopathy may exist, the latter referring to a clinical state of altered mental status that can manifest as confusion, disorientation, or other cognitive impairment, with or without evidence of brain tissue inflammation; encephalopathy can be triggered by a number of metabolic or toxic conditions but occasionally occurs in response to certain infectious agents, such as *Bartonella henselae* and influenza virus.[6]

Of all the pathogens reported to cause encephalitis, most are viruses that may be associated with specific clinical and neuroimaging findings that suggest their diagnosis.[4,5] Unilateral temporal lobe encephalitis is classically caused by HSV, leading to clinical manifestations characterized by personality changes, altered mentation, a decreasing level of consciousness, seizures, and focal neurologic findings (e.g., dysphasia, weakness, and paresthesias). Bilateral temporal lobe involvement or lesions outside the temporal lobe, insula, or cingulate are less likely caused by HSV.[7]

Other herpesviruses that cause encephalitis during any season include VZV, cytomegalovirus (CMV), and human herpesvirus 6 and are usually seen more frequently in immunosuppressed individuals. Arboviruses (e.g., West Nile, eastern equine, St. Louis, La Crosse, and Japanese encephalitis viruses) and respiratory viruses can present with a thalamic and basal ganglia encephalitis presenting with tremors, including Parkinsonism features.[8] Patients with WNV infection typically present between June and October, whereas respiratory viruses are usually present in children during the winter season. HIV can present as an encephalitis in patients not receiving antiretroviral therapy or can present as a CD8 encephalitis in those with immune reconstitution while on antiretroviral therapy.[9] Rabies virus is still a frequent cause of encephalitis in Asia (India especially) and in Africa. Enteroviruses are rare causes of encephalitis.[4,5]

Nonviral causes of encephalitis include *Mycobacterium tuberculosis*, *L. monocytogenes, Rickettsia, Ehrlichia* spp., *Bartonella* spp., *Mycoplasma pneumoniae*, and *Toxoplasma gondii* (more often seen in transplant patients with *Toxoplasma* encephalitis).[4] Several free-living amebae (i.e., *N. fowleri*, *Acanthamoeba* spp., and *Balamuthia mandrillaris*) may cause a fatal encephalitis, usually during the summer months.[4] Other epidemiologic clues that may be helpful in directing the investigation for an etiologic agent in patients with encephalitis include geographic locale, prevalence of disease in the local community, travel history, recreational activities, occupational exposure, insect contact, animal contact, vaccination history, and immune status of the patient.[4,5] In many cases of encephalitis (32%–75%) the etiology remains unknown, however, despite extensive diagnostic testing.[4,5,10] In addition, it is important to distinguish between infectious encephalitis and autoimmune encephalitis (antibody-mediated, postinfectious, or postimmunization acute disseminated encephalomyelitis). These latter syndromes are presumed to be mediated by an immunologic response to an antecedent antigenic stimulus provided by the infecting microorganism or immunization.[4,10] Anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis[11,12] is the most common cause of antibody-associated encephalitis and is typically seen in young females with an associated ovarian teratoma. Anti-NMDAR encephalitis has now also been associated with both HSV and VZV infections.[13]

Focal Central Nervous System Syndromes

The clinical presentation in patients with focal CNS lesions (e.g., brain abscess, subdural empyema, and epidural abscess) depends on the route of spread of the infection to the CNS, location of the lesion, and severity of increased intracranial pressure (ICP) (see Chapters 90 and 91). Patients develop brain abscesses via contiguous spread (e.g., from sinusitis, otitis media, or mastoiditis), hematogenous dissemination (e.g., from the lung or in patients with infective endocarditis), or trauma. Initial clinical manifestations include headache, nausea, vomiting, and focal neurologic findings. Although patients may be brought to medical attention after development of a seizure or alteration in consciousness, fever is usually seen in less than 50% of patients. In patients with fungal brain abscess caused by *Aspergillus* spp. or the Mucorales, the clinical presentation may be that of a stroke syndrome because of the propensity of these organisms to invade blood vessels. In patients with focal infections that compress the spinal cord, such as epidural abscess or subdural empyema, the sequence of back pain, radiculopathy, and motor and sensory findings may eventually progress to complete paralysis, a clinical manifestation that is irreversible unless there is emergency intervention (see Chapter 91).

LUMBAR PUNCTURE

Lumbar puncture, with removal and analysis of CSF, is an essential procedure in the diagnosis of meningitis and encephalitis.[1,14] In the performance of a lumbar puncture the patient and the needle should be properly positioned to obtain adequate amounts of CSF; the patient is placed in either the lateral recumbent position on a firm surface with the back at the edge of the table and perpendicular to the table surface or sitting with the back curved.[14] The patient is first properly positioned, then the clinician wears sterile gloves and a mask and cleans the puncture site with antiseptic solution. Once the iodine solution has dried, 2 mL of 1% lidocaine without epinephrine is injected between the third and fourth lumbar vertebrae; once numb, a spinal needle (preferably 20 gauge or less) is inserted in the midline perpendicular to the back. After needle insertion, frequent removal of the stylet can determine whether the subarachnoid space has been entered. At that point a "pop" is felt, indicating penetration of the needle across the ligamentum flavum.[15]

Numerous complications have been associated with performance of lumbar puncture,[1,15] ranging from mild discomfort with insertion of the spinal needle to life-threatening conditions. The most common complication after lumbar puncture is headache, which is generally observed in 10% to 25% of patients; the headache is characteristically absent when the patient is recumbent and appears rapidly when the patient stands. The headache is believed to be secondary to low CSF pressure as a result of continued leakage of CSF at the site of the lumbar puncture. The risk of headache may be reduced by using smaller-gauge needles (20 gauge or less) or by placing the patient in the prone position for several hours after the procedure, although it is unclear whether the latter maneuver is effective in reducing the likelihood of headache after lumbar puncture. A recommendation from the American Academy of Neurology supports the use of atraumatic (Sprotte or Pajunk) needles, rather than the standard (Quincke) needle, to reduce the risk of postlumbar puncture headache.[15] Reinsertion of the stylet before needle removal has also been shown to decrease the risk of headache.[15] The headache usually resolves within hours to days after the procedure. Persistent headache can be treated by use of a "blood patch," in which some of the patient's own venous blood is injected outside the meninges at the site of the lumbar puncture; this procedure seals the site of CSF leakage.[15] In a recent systematic review and meta-analysis, use of atraumatic needles was associated with a decrease in the incidence of postdural puncture headache, need for intravenous fluid or controlled analgesia, need for epidural blood patch, any headache, nerve root irritation, and hearing disturbance, and it had similar efficacy to conventional needles.[16] This study suggests that atraumatic needles should be used in patients requiring lumbar puncture.[17]

Infection is a very rare complication after lumbar puncture (1/50,000 procedures), even in patients with concomitant bacteremia.[1,15] Although there have been conflicting studies on the risk of subsequent meningitis in patients who are bacteremic at the time of lumbar puncture, the importance of performing a diagnostic lumbar puncture in the appropriate clinical setting greatly outweighs any minor risk that the procedure itself might induce meningitis in a bacteremic patient. Lumbar puncture should not be performed in patients with established local infection in the lumbar space (e.g., spinal epidural abscess, spinal subdural empyema, or superficial or deep paraspinal infection); in these cases, CSF analysis should be obtained under fluoroscopic guidance via high cervical or cisternal puncture.[15]

Local bleeding is a more common complication after lumbar puncture[1,15]; up to 20% of patients have a so-called traumatic tap.[1,15] Bleeding may occur from inadvertent puncture of the venous plexuses located dorsally and ventrally to the spinal dura or secondary to injury to vessels that accompany the cauda equina. This local bleeding rarely does harm to the patient, although patients with coagulation disturbances or who are receiving anticoagulants may develop continued bleeding with the development of spinal subdural or epidural hematomas, which may compress the cauda equina and produce permanent neurologic injury. This complication is extremely rare, even in patients with coagulopathies, with only 35 cases described in the literature over the last 42 years.[18]

The most feared complication after lumbar puncture is brain herniation, which may occur in a patient with an elevation of ICP.[1,15] In patients who undergo lumbar puncture there is normally a mild, transient reduction of lumbar CSF pressure that is rapidly communicated throughout the subarachnoid space. In patients with bacterial meningitis and suspected severe intracranial hypertension or impending herniation, a 22- or 25-gauge spinal needle should be used, with careful observation for several hours after removal of CSF; monitoring and treatment of increased ICP may need to be considered (see later). In patients who have an intracranial space-occupying lesion, particularly one located in the posterior fossa, there is already a relative pressure gradient (with

downward displacement of the cerebrum and brainstem) that can be increased by lumbar puncture and precipitate brain herniation.

Certain patients should undergo neuroimaging studies (i.e., computed tomography [CT] or magnetic resonance imaging [MRI]) before lumbar puncture if there is a suspicion that their neurologic presentation may be secondary to an intracranial mass lesion with accompanying mass effect. The Infectious Diseases of America (IDSA) guidelines recommend that patients with suspected meningitis with the following characteristics should get a cranial imaging study before the lumbar puncture: immunocompromised state (HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation), history of CNS disease (mass lesion, stroke, or focal infection), new-onset seizure, abnormal level of consciousness, papilledema, or focal neurologic deficit (including dilated, nonreactive pupil; abnormalities of ocular motility; abnormal visual fields; gaze palsy; or arm or leg drift).[19] However, adherence to the IDSA guidelines is low (40%), with no clinical benefit in those patients undergoing cranial imaging without an indication.[20] Other guidelines (from the United Kingdom [UK], Europe, and Sweden) are more restrictive, with some guidelines (UK and Sweden) not recommending cranial imaging in immunosuppressed individuals but recommending cranial imaging only with focal neurologic deficits or finding a Glasgow Coma Scale score <12 in the UK or <10 in Europe and cerebral herniation signs in Sweden.[21,22,23] It has been suggested, however, that a normal CT scan does not always mean performance of a lumbar puncture is safe. Certain clinical signs of impending herniation, such as a deteriorating level of consciousness (particularly a Glasgow Coma Scale score ≤11), brainstem signs (including pupillary changes, posturing, or irregular respirations), or a very recent seizure, may be predictive of patients in whom lumbar puncture should be delayed.[24]

Opening Pressure and Appearance

In the evaluation of CNS infections via lumbar puncture, numerous parameters should be assessed.[1,15] CSF opening pressure is measured with an air-water manometer; in adults placed in the lateral decubitus position, the normal CSF opening pressure ranges from 50 to 195 mm H_2O; values <150 mm H_2O are clearly normal, and those >200 mm H_2O are abnormal. Pressure measured with the patient prone, as is done for fluoroscopic lumbar puncture, should be calculated as the distance from the CSF meniscus to the location of the patient's right ventricle. The CSF specimen should be sent to the laboratory for analysis (Table 86.1). The CSF is normally clear and colorless but may appear cloudy or turbid in patients with increased concentrations of WBCs (>200/mm^3), red blood cells (RBCs, >400/mm^3), bacteria (>10^5 colony-forming units/mL), or protein. In patients with a traumatic tap an initially bloody CSF (present when there are at least 6000 RBCs/mm^3) should clear as flow of CSF continues.

Xanthochromia, a yellow or yellow-orange supernatant of centrifuged CSF, is usually a result of RBC lysis and the presence of oxyhemoglobin, methemoglobin, and bilirubin; it characteristically appears 2 to 4 hours after RBCs have entered the subarachnoid space, although it has occasionally been seen for 12 hours.[1,15] The presence of xanthochromia distinguishes CSF that is bloody secondary to subarachnoid hemorrhage from CSF that is bloody secondary to a traumatic lumbar puncture, in which the centrifuged supernatant is clear. Xanthochromia may also be observed with very high CSF protein concentrations that can cause the CSF to clot (Froin syndrome, due to meningitis or spinal block) or as a consequence of systemic hyperbilirubinemia (>10–15 mg/dL).[15] In patients with meningitis, specific CSF results may vary depending on the infectious agent (Table 86.2). For additional information on CSF results for specific etiologic agents of meningitis and encephalitis, see the subsequent chapters in this section. Details of some CSF parameters are reviewed as follows.

Cell Count

The normal CSF WBC count in children and adults is 0 to 5/mm^3. CSF WBC counts in term neonates may be 32/mm^3 (mean, 8–9/mm^3), although by 1 month of age normal CSF has less than 10 WBCs/mm^3. Elevated CSF concentrations of WBCs are seen in patients with meningitis, encephalitis, and parameningeal foci of infection (e.g., space-occupying lesions).[1,15] False-positive elevations of CSF WBC counts can be found after traumatic lumbar puncture or in patients with intracerebral

TABLE 86.1 Tests of Cerebrospinal Fluid in Patients With Suspected Central Nervous System Infection

Routine Tests
White blood cell count with differential
Red blood cell count[a]
Glucose concentration[b]
Protein concentration
Gram stain
Bacterial culture
Selected Specific Tests Based on Clinical Suspicion
Viral culture[c]
Smears and culture for acid-fast bacilli
Venereal Disease Research Laboratory
India ink preparation
Cryptococcal polysaccharide antigen
Fungal culture
Antibody tests (IgM or IgG, or both)[d]
Nucleic acid amplification tests (e.g., polymerase chain reaction)[e]
Cytology[f]
Flow cytometry

[a]Should be checked in the first and last tubes; in patients with a traumatic tap, there should be a decrease in the number of red blood cells (RBCs) with continued flow of cerebrospinal fluid (CSF). See text for the formula for determining whether the numbers of CSF RBCs and white blood cells are consistent with a traumatic tap.
[b]Compare with serum glucose drawn just before lumbar puncture.
[c]Yield of viral culture may be low (see Chapters 87 and 89).
[d]May be useful for specific causes of meningitis and encephalitis (see Chapters 87, 88, and 89).
[e]Most useful for specific viral causes of encephalitis and causes of chronic meningitis; see text and Chapters 88 and 89 for details.
[f]In patients with suspected malignancy.

TABLE 86.2 Typical Cerebrospinal Fluid Findings in Patients With Selected Infectious Causes of Meningitis

CAUSE OF MENINGITIS	WHITE BLOOD CELL COUNT (cells/mm^3)	PRIMARY CELL TYPE	GLUCOSE (mg/dL)	PROTEIN (mg/dL)
Viral	50–1000	Mononuclear[a]	>45	<200
Bacterial	1000–5000[b]	Neutrophilic[c]	<40[d]	100–500
Tuberculous	50–300	Mononuclear[e]	<45	50–300
Cryptococcal	20–500[f]	Mononuclear	<40	>45

[a]May be neutrophilic early in presentation (see Chapter 87).
[b]Range from <100 to >10,000 cells/mm^3.
[c]About 10% of patients have cerebrospinal fluid (CSF) lymphocyte predominance.
[d]Should always be compared with a simultaneous serum glucose; ratio of CSF to serum glucose is ≤0.4 in most cases (see Chapter 87).
[e]May see a "therapeutic paradox," in which a mononuclear predominance becomes neutrophilic during antituberculous therapy.
[f]Greater than 75% of patients with acquired immunodeficiency syndrome have <20 cells/mm^3.

or subarachnoid hemorrhage in which RBCs and WBCs are introduced into the subarachnoid space (e.g., chemical meningitis). In these instances the following formula should be used as a correction factor for the true WBC count in the presence of CSF RBCs[1]:

$$\text{Adjusted WBCs in CSF} = \text{Actual WBCs in CSF} - \frac{\text{WBC in blood} \times \text{RBCs in CSF}}{\text{RBCs in blood}}$$

In the above equation, the amount being subtracted is the predicted CSF WBC count that would occur if all the CSF WBCs were the result of blood contamination.[1]

Generalized seizures may also induce a transient CSF pleocytosis that is primarily neutrophilic, although the total WBC count should not exceed 80/mm^3. Pleocytosis should not be ascribed to seizure activity alone, however, unless the fluid is clear and colorless, the opening pressure and CSF glucose are normal, the CSF Gram stain is negative, and the patient has no clinical evidence of CNS infection.[1] In patients with CSF pleocytosis, differential counts should be performed; a neutrophilic, mononuclear, or eosinophilic predominance may be suggestive of certain etiologies in the right clinical setting (see Table 86.2 and Chapters 88 and 89). Although CSF pleocytosis is suggestive of inflammation of the brain and/or meninges, the absence of CSF pleocytosis does not exclude the diagnosis of encephalitis.[25,26]

Glucose and Protein

CSF hypoglycorrhachia is seen in many CNS infections. The pathogenesis of CSF hypoglycorrhachia is multifactorial and may include an increased rate of macrovesicular glucose transport across arachnoid villi, increased glycolysis by leukocytes and bacteria, increased metabolic rate of the brain and spinal cord, or inhibition of glucose entry into the subarachnoid space caused by alterations in the membrane carrier system responsible for glucose transfer from blood to CSF.[15,27] The actual CSF glucose concentration may be falsely low in the presence of hypoglycemia, or may be incorrectly interpreted as normal when the patient is hyperglycemic (e.g., in diabetic patients). The CSF glucose should always be compared with a simultaneous serum glucose that is drawn before lumbar puncture; the normal lumbar CSF-to–serum glucose ratio is approximately 0.6, and ratios <0.5 should be considered abnormal.[15] Unfortunately, only 13% of patients with community-acquired meningitis have a simultaneous serum and CSF glucose performed.[27] An absolute CSF glucose <45 mg/dL can be used to define hypoglycorrhachia, as hypoglycemia and hyperglycemia are rarely seen in patients with meningitis.[27]

The CSF protein concentration is also elevated in numerous CNS infections, presumably because of disruption of the blood-brain barrier, manifested morphologically by separation of intercellular tight junctions and increased numbers of pinocytotic vesicles in microvascular endothelial cells.[1] Lumbar CSF protein concentrations >50 mg/dL and ventricular CSF concentrations >15 mg/dL are considered abnormal. A CSF protein >100 mg/dL is a risk factor for an urgent treatable cause of meningitis in adults, and a CSF protein <100 mg/dL is a predictor for enteroviral meningitis in children.[28,29] An elevated CSF protein may also be observed in various infectious and noninfectious disorders of the CNS. In patients with a traumatic lumbar puncture the true CSF protein concentration is determined by subtracting 1 mg/dL of protein for every 1000 RBCs/mm^3, although these determinations must be made in the same CSF tube.[15]

Other Cerebrospinal Fluid Tests

Additional studies of CSF may be useful in determining a specific etiologic diagnosis in patients with meningitis and encephalitis.[1] Cultures are important in attempts to identify a specific etiologic agent, but, depending on the pathogen, larger CSF volumes may be needed to increase the yield of a positive culture (e.g., for *M. tuberculosis* or fungi), and CSF cultures may require prolonged incubation and special techniques for isolation of specific pathogens (see Chapters 87–89). In some cases simple stains of CSF specimens may establish the etiologic diagnosis.

In patients with suspected bacterial meningitis, CSF Gram stain may provide a clue as to the etiologic diagnosis (see Chapter 87).[1] The CSF Gram stain is positive in 60% to 90% of patients with acute bacterial meningitis, although this sensitivity varies depending on the concentration of microorganisms in the CSF and the specific causative bacteria. Not all specialized stains of CSF to identify specific microorganisms are as sensitive as the Gram stain, however. In patients with tuberculous meningitis, less than 15% to 25% of specimens are smear-positive by acid-fast stain and 20% of patients with tuberculous meningitis have persistently negative CSF cultures. In patients with spirochetal meningitis (i.e., caused by *Treponema pallidum* or *Borrelia burgdorferi)* and *Toxoplasma* encephalitis, there are no effective specialized stains that identify these organisms in CSF; in these cases serum or CSF antibody studies are most often used to aid in the diagnosis (see Chapters 88 and 89).

CSF India ink examination is positive in 50% to 75% of patients with cryptococcal meningitis, and the yield increases to 88% in patients with AIDS. The most important CSF test in the diagnosis of cryptococcal meningitis is the CSF test for detection of cryptococcal polysaccharide antigen. The presence of virus-specific immunoglobulin M (IgM) in CSF is usually indicative of CNS disease because IgM antibodies do not readily diffuse across the blood-brain barrier; detection of IgM antibodies from patients with presumed flavivirus encephalitis is considered diagnostic of neuroinvasive disease.[4]

Nucleic acid amplification tests, such as PCR, of CSF are highly sensitive and specific for the diagnosis of many CNS infections and may be useful in providing a rapid diagnosis.[4,5,15] In patients with herpes simplex encephalitis CSF PCR is 96% to 98% sensitive and 95% to 99% specific in adult patients[30]; CSF PCR results are positive early in the disease course and remain positive during the first week of therapy, although false-negative results may occur if hemoglobin or other inhibitors are present in CSF. An initially negative CSF PCR result for HSV may become positive if the test is repeated 1 to 3 days after the initiation of treatment[4,31]; in undiagnosed cases in which patients have clinical or neuroimaging features suggestive of HSV encephalitis, consideration should be given to repeating the PCR for HSV 3 to 7 days later on a second CSF specimen.[4] Diagnosis of CMV encephalitis by PCR has a high sensitivity and specificity for the diagnosis of CNS involvement[32]; the absence of CMV DNA by PCR has a high negative predictive value. Nucleic acid amplification with reverse-transcriptase PCR has also been found to be highly sensitive (86%–100%) and specific (92%–100%) for the diagnosis of enteroviral infections of the CNS,[15] and it has high specificity for the diagnosis of other viral causes of CNS infections, such as VZV and JC virus.[15,29]

The clinical utility of PCR in patients with bacterial meningitis has been investigated with the use of a broad range of bacterial primers (i.e., broad-based PCR).[15,33] In one study[33] the broad range was highly sensitive and was able to detect pathogens up to 1 week after antibiotic therapy. A rapid (<1 hour) multiplex PCR that detects, with high sensitivity and specificity, 14 common causes of meningitis and encephalitis is now widely available.[34] This panel includes testing for six bacteria (*S. pneumoniae, N. meningitidis, Streptococcus agalactiae, Haemophilus influenzae, L. monocytogenes, Escherichia coli* K1), seven viruses (HSV-1 and HSV-2, human herpesvirus 6, CMV, enterovirus, parechovirus, VZV), and two fungi (*Cryptococcus gattii/neoformans*). Use of PCR to detect the fragments of mycobacterial DNA in CSF has also been used for rapid diagnosis of tuberculous meningitis.[35] The sensitivity for the different *Mycobacterium tuberculosis* (MTB) PCR technologies ranges from 55.8% to 87.6%, with recent nested MTB PCR showing sensitivity and specificity up to 89% and 100%, respectively.[36] In addition, in a recent study in 129 HIV-infected adults with suspected tuberculous meningitis, use of Xpert Ultra, a new, fully automated, nested real-time PCR assay for the GeneXpert (Cepheid; Sunnyvale, CA) platform, revealed that the Xpert Ultra sensitivity was 70% for probable or definite tuberculous meningitis compared with 43% for Xpert and 43% for culture.[37] At present, however, with the currently available MTB PCRs a negative CSF PCR result cannot be used to exclude the diagnosis of tuberculous meningitis. Although these molecular diagnostic methods have utility in the identification of the causative microorganism, they are often not available in resource-poor settings.[35] More information on the use of specialized CSF tests to establish an etiologic diagnosis

and use of other adjunctive tests in patients with meningitis and encephalitis can be found in Chapters 87 to 89.

NEUROIMAGING STUDIES

The use of neuroimaging studies, specifically CT and MRI, has been invaluable in localizing infectious processes within the CNS and in assessing response to therapy.[38,39] With CT scanning, areas of bone and blood appear as areas of high signal intensity compared with brain and CSF, which appear as areas of low signal intensity. After intravenous (IV) administration of an iodinated contrast agent, increased intensity (i.e., contrast enhancement) is seen in areas of blood-brain barrier breakdown, increasing the sensitivity for the diagnosis of certain abnormalities (e.g., brain abscesses). MRI directly generates images in all three planes (axial, coronal, and sagittal) for optimal evaluation of brain morphology and pathology; MRI can also provide information about blood flow within arteries and veins and shows enhancement of specific lesions after IV administration of gadolinium diethylenetriaminepentaacetic acid. Given the higher sensitivity of MRI compared with CT, MRI has become the preferred neuroimaging modality in the evaluation of virtually all patients with suspected CNS infection. In addition to conventional MRI sequences, recent advances have added further sensitivity and specificity to the diagnosis of brain infection.[38] These include diffusion-weighted imaging (DWI), diffusion tensor imaging, susceptibility-weighted imaging (SWI), perfusion-weighted imaging (PWI), and ^{1}H magnetic resonance spectroscopy. However, the availability of MRI, particularly with high-magnetic field strength, is more limited, especially in the developing world. These modalities are reviewed in further detail in subsequent chapters of this section, based on specific clinical syndromes, but some examples are given here.

The most important and specific neuroimaging technique in patients with HSV encephalitis is MRI with contrast enhancement, which shows lesions earlier than does CT[4]; MRI may also be useful in other causes of viral encephalitis (e.g., basal ganglia involvement in patients with WNV encephalitis) (see Chapter 89). DWI is superior to conventional MRI for the detection of early signal abnormalities in viral encephalitis caused by HSV, enterovirus 71, and WNV.[38,39,40] Neuroimaging studies are less important in the diagnosis of patients with bacterial meningitis but may be useful in patients who are not responding as expected, that is, have persistent or prolonged fever, clinical evidence of increased ICP, focal neurologic findings, new or recurrent seizures, enlarging head circumference (in neonates), persistent neurologic dysfunction, or persistently abnormal CSF parameters or cultures.[1] MR angiography and PWI in patients with bacterial meningitis may show vascular complications, such as vasculitis, including focal stenosis and irregularity of the major intracranial arteries as well as infectious dural sinus thrombosis[38,39]; SWI may visualize hemorrhages within the infarcted regions with high sensitivity.

MRI is more sensitive than CT in the detection of focal CNS infections and has the advantages of early detection of cerebritis, cerebral edema with greater contrast between edema and adjacent brain tissue, more conspicuous spread of inflammation into the ventricles and subarachnoid space, and earlier detection of satellite lesions (see Chapter 90). Contrast enhancement with gadolinium provides the added advantage of clear differentiation of the central abscess, surrounding enhancing rim, and cerebral edema surrounding the abscess. On T2-weighted images, the zone of edema that surrounds the abscess is one of high signal intensity. The key to distinguishing abscess from other cystic intracranial processes (e.g., necrotic tumors) is DWI[40]; pus in the abscess has restricted diffusion and appears DWI hyperintense. In AIDS patients with positive immunoglobulin G (IgG) antibody titers to *T. gondii*, the detection of multiple ring-enhancing lesions by CT with contrast enhancement or MRI is enough evidence to initiate a trial of anti-*Toxoplasma* chemotherapy[38] (see Chapter 90); CT or MRI is repeated in 10 to 14 days to document a clinical response. Advances in neuroimaging technology may refine further the approach to patients with CNS infections.

MANAGEMENT

Antimicrobial Therapy

Many factors influence the choice of a specific antimicrobial agent in the therapy of CNS infections. These factors have been best studied in experimental animal models of infections to evaluate use of antibacterial agents in the treatment of bacterial meningitis.[1,41] One important factor is the penetration of the antimicrobial agent into the CSF, to attain adequate drug concentrations to kill the meningeal pathogen rapidly and effectively. Drug penetration into CSF depends on the status of the blood-brain barrier, which is disrupted in the presence of meningeal inflammation. Some agents (e.g., corticosteroids) may reduce meningeal inflammation and reduce blood-brain barrier penetration of antimicrobial agents even though appropriate CSF vancomycin concentrations were documented in patients treated with adjunctive dexamethasone in one study.[42] Entry of antimicrobial agents into CSF is also enhanced by drugs that have a low molecular weight, low degree of ionization at physiologic pH, high lipid solubility, and low degree of protein binding.[1,41]

When the antimicrobial agent penetrates the CSF, it must exhibit rapid bactericidal activity against the infecting pathogen because bacterial meningitis is an infection in an area of impaired host resistance. A final factor that contributes to response to antimicrobial therapy is pharmacodynamics, which is concerned with the time course of antimicrobial activity at the site of infection; these factors and whether the specific agent kills by concentration-dependent or time-dependent killing are important to determine the dosing regimen for optimal effectiveness. Selection of empirical antimicrobial therapy must also be based on likely in vitro susceptibility.[1,19,41] In addition, intraventricular or intrathecal therapy may be required for eradication of resistant pathogens in patients with health care–associated ventriculitis and meningitis.[43] These principles are reviewed in further detail in Chapters 87 and 92.

Many of the principles for treatment of bacterial meningitis may also apply to treatment of other nonbacterial etiologies of meningitis and encephalitis. In addition, experimental and clinical studies have examined the penetration of specific antimicrobial agents into brain abscesses, which may be important in the antimicrobial therapy of these infections. In the therapy of focal intracranial infections, clinicians often rely on agents that are known to have efficacy in experimental animal models, which includes extrapolating data from animal models of meningitis, and based on anecdotal case series or case reports. This approach is reasonable because these infections are uncommon, and randomized trials of specific agents are not likely to be performed.

Surgical Therapy

Many patients with focal CNS infections require surgical therapy for optimal management (see Chapters 90 and 91).[44] Drainage of brain abscesses, subdural empyema, and epidural abscess is crucial to establishing a microbiologic diagnosis and to ensuring a good outcome by relieving the increased ICP and neurologic findings that are associated with these disorders. Aspiration can be performed via guidance with neuroimaging modalities (i.e., CT or MRI), which allows the surgeon rapid, accurate, and safe access to virtually any intracranial or parameningeal focus. Open craniotomy may be required for extensive intracranial infections that cannot be adequately drained via bur-hole aspiration (e.g., in patients with cranial subdural empyema). Although some patients with focal CNS infections can be treated with antimicrobial therapy alone, these patients must be selected carefully and followed to ensure that neurologic dysfunction does not develop or progress.

Adjunctive Therapy

The morbidity and mortality in patients with CNS infections remain unacceptably high. Because CNS infections can be complicated by cerebral edema and increased ICP (with the potential for brain herniation), various adjunctive strategies have been examined for their efficacy in CNS infections. Among the best-studied agents are corticosteroids. Adjunctive dexamethasone, given concomitant with or just before the first antimicrobial dose, improves outcomes in infants and children with *H. influenzae* type b, and perhaps pneumococcal meningitis, and in adults with pneumococcal meningitis (see Chapter 87).[1,19,44] Adjunctive corticosteroids may not be beneficial, however, in patients with bacterial meningitis in the developing world, most likely because of their delayed presentation.[45] Corticosteroids may also be beneficial in patients with focal intracranial infections and cerebral edema associated with significant mass effect.[44] Steroids may be beneficial in reduction of edema, leading

to improvement of symptoms and signs of neurologic dysfunction until more definitive interventions can be performed.

Other adjunctive modalities in treatment of CNS infections are directed toward reduction of increased ICP.[44,46] ICP can be reduced by decreasing total intracranial volume (by withdrawal of CSF via ventricular drainage), reduction of cerebral tissue volume (by osmotic dehydration), removal or decompression of an intracranial mass, or a decompressive craniectomy in refractory cases.[46] Although it should be noted that randomized studies of various strategies to lower ICP in patients with CNS infections have not been performed, some maneuvers may be beneficial.[45,46] Head elevation of 30 degrees is considered standard, and other factors that might increase ICP, such as pain, bladder distention, and agitation, should be avoided. Hyperventilation (to maintain the partial pressure of carbon dioxide in arterial blood at 27–30 mm Hg), which causes vasoconstriction and reduction in intracerebral volume, may also be used to reduce ICP, although it should be used only as a short-term intervention to quickly reduce ICP when it is dangerously elevated because it may induce cerebral ischemia (see Chapter 87). Hyperosmolar agents decrease ICP by making the intravascular space hyperosmolar relative to the brain, permitting movement of water from the brain tissue to the intravascular compartment. However, a controlled trial from Malawi of adjunctive glycerol in adult patients with bacterial meningitis showed that it was harmful and increased mortality.[47] Similarly, a clinical trial of hypothermia (to reduce ICP) in bacterial meningitis showed a trend toward worse clinical outcomes.[48] In patients who continue to have elevated ICP despite the aforementioned interventions, high-dose barbiturate therapy may be considered, although this treatment modality is associated with multiple complications, including myocardial depression and hypotension. One observational study, which reported findings on the use of measurements of continuous ICP and cerebral perfusion pressure in the treatment of patients with severe bacterial meningitis, indicated that the mean ICP was significantly higher, and the cerebral perfusion pressure was markedly decreased, in patients who did not survive despite appropriate treatment.[49]

Seizures may occur in patients with CNS infections and must be managed quickly and aggressively to avoid permanent anoxic ischemic changes.[1,45,46] Status epilepticus that is continuous for 90 minutes or more can lead to permanent neurologic injury. Short-acting anticonvulsants with a rapid onset of action (e.g., lorazepam or diazepam) should be given, followed by a long-acting agent, such as phenytoin. If these maneuvers fail to terminate the seizure, the patient should be intubated, mechanically ventilated, and treated with phenobarbital.

Fluid management is crucial in patients with CNS infections.[1,50] Some patients may be volume depleted as a result of decreased oral intake, vomiting, and diarrhea. In these patients IV fluids are required to maintain systemic and cerebral perfusion. Hyponatremia (serum sodium <135 mEq/L) may occur in patients with CNS infections, attributed to the syndrome of inappropriate secretion of antidiuretic hormone. There is some evidence to support the use of IV maintenance fluids in the first 48 hours in patients with bacterial meningitis[50]; although there is insufficient evidence to guide this practice, adult patients with meningitis should be treated with the goal of attaining a normovolemic state.[1,50]

Aggressive treatment of these complications in the critical care setting has improved the neurologic outcome of patients with CNS infections. The definitive treatment of specific infectious syndromes and the etiologic agents that cause them are reviewed in detail in the following chapters of this section.

References

1. Tunkel AR. *Bacterial Meningitis*. Philadelphia: Lippincott Williams & Wilkins; 2001.
2. Sulaiman T, Salazar L, Hasbun R. Acute vs subacute community-acquired meningitis: analysis of 611 patients. *Medicine (Baltimore)*. 2017;96:e7984.
3. Kainer MA, Reagan DR, Nguyen DB, et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. *N Engl J Med*. 2012;367:2194–2203.
4. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the International Encephalitis Consortium. *Clin Infect Dis*. 2013;57:1114–1128.
5. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47:303–327.
6. Weitkamp JH, Spring MD, Brogan T, et al. Influenza A virus-associated acute necrotizing encephalopathy in the United States. *Pediatr Infect Dis J*. 2004;23:259–263.
7. Chow FC, Glaser CA, Sheriff H, et al. Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics. *Clin Infect Dis*. 2015;60:1377–1383.
8. Beattie GC, Glaser CA, Sheriff H, et al. Encephalitis with thalamic and basal ganglia abnormalities: etiologies, neuroimaging, and potential role of respiratory viruses. *Clin Infect Dis*. 2013;56:825–832.
9. Lescure F X, Moulignier A, Savatovsky J, et al. CD8 encephalitis in HIV-infected patients receiving cART: a treatable entity. *Clin Infect Dis*. 2013;57:101–108.
10. Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults—association of British neurologists and British Infection Association national guidelines. *J Infect*. 2012;64:347–373.
11. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63–74.
12. Gable MS, Sheriff H, Dalmau J, et al. The frequency of autoimmune *N*-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies of young individuals enrolled in the California encephalitis project. *Clin Infect Dis*. 2012;54:899–904.
13. Solis N, Salazar L, Hasbun R. Anti-NMDA receptor antibody encephalitis with concomitant detection of varicella zoster virus. *J Clin Virol*. 2016;83:26–28.
14. Straus SE, Thorpe KE, Holroyd-Leduc J. How do I perform a lumbar puncture and analyze the results to diagnose bacterial meningitis? *JAMA*. 2006;296:2012–2022.
15. Hasbun R. Cerebrospinal fluid in central nervous system infections. In: Scheld WM, Whitley RJ, Marra CM, eds. *Infections of the Central Nervous System*. 4th ed. Philadelphia: Lippincott Williams & Wilkins.; 2014:4–23.
16. Nath S, Koziarz A, Badhiwala JH, et al. Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. *Lancet*. 2018;391:1197–1204.
17. van de Beek D, Brouwer MC. Atraumatic lumbar puncture needles: practice needs to change. *Lancet*. 2018;391:1128–1129.
18. Brown MW, Yilmaz TS, Kasper EM. Iatrogenic spinal hematoma as a complication of lumbar puncture: what is the risk and best management plan? *Surg Neurol Intern*. 2016;7:S581–S589.
19. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
20. Salazar L, Hasbun R. Cranial imaging before lumbar puncture in adults with community-acquired meningitis: clinical utility and adherence to the Infectious Diseases Society of America guidelines. *Clin Infect Dis*. 2017;64:1657–1662.
21. McGill F, Heyderman RS, Michael BD, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. *J Infect*. 2016;72:405–438.
22. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microb Infect*. 2016;22:S37–S62.
23. Glimaker M, Johansson B, Grindborg O, et al. Adult bacterial meningitis: earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture. *Clin Infect Dis*. 2015;60:1162–1169.
24. Joffe AR. Lumbar puncture and brain herniation in acute bacterial meningitis: a review. *J Intensive Care Med*. 2007;22:194–207.
25. Erdem H, Ozturk-Engin D, Cag Y, et al. Central nervous system infections in the absence of cerebrospinal fluid pleocytosis. *Int J Infect Dis*. 2017;65:107–109.
26. Jakob NJ, Lenhard T, Schnitzler P, et al. Herpes simplex virus encephalitis despite normal cell count in the cerebrospinal fluid. *Crit Care Med*. 2012;40:1304–1308.
27. Shrikanth V, Salazar L, Khoury N, et al. Hypoglycorrhachia in adults with community-acquired meningitis: etiologies and prognostic significance. *Int J Infect Dis*. 2015;39:39–43.
28. Hasbun R, Bijlsma M, Brouwer MC, et al. Risk score for identifying adults with CSF pleocytosis and negative CSF gram stain at low risk for an urgent treatable cause. *J Infect*. 2013;67:102–110.
29. Zakhour R, Aguilera E, Hasbun R, et al. Risk classification for enteroviral infection in children with meningitis and a negative gram stain. *Pediatr Emerg Care*. 2018;34:791–796.
30. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. *Neurother*. 2016;13:493–508.
31. Weil AA, Glaser CA, Amad Z, et al. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. *Clin Infect Dis*. 2002;34:1154–1157.
32. Wildemann B, Haas J, Lynen N, et al. Diagnosis of cytomegalovirus central nervous system disease in AIDS patients by quantitation of cytomegalovirus genomes in cells of cerebrospinal fluid. *Neurology*. 1998;50:693–697.
33. Brink M, Welinder-Olsson C, Hagberg L. Time window for positive cerebrospinal fluid broad-range bacterial PCR and *Streptococcus pneumoniae* immunochromatographic test in acute bacterial meningitis. *Infect Dis*. 2015;47:869–877.
34. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol*. 2016;54:2251–2261.
35. Leonard J. Central nervous system tuberculosis. *Microbiol Spectrum*. 2017;5.
36. Sun Y, Chen J, Li J, et al. Novel approach based on one-tube nested PCR and a lateral flow strip for highly sensitive diagnosis of tuberculous meningitis. *PLoS ONE*. 2017;12:e0186985.
37. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet*. 2018;18:68–75.
38. Swinburne NC, Bansal AG, Aggarwal A, et al. Neuroimaging in central nervous system infections. *Curr Neurol Neurosc Rep*. 2017;17:49.
39. Nickerson JP, Richner B, Santy K, et al. Neuroimaging of pediatric intracranial infection—part 1: techniques and bacterial infections. *J Neuroimaging*. 2012;22:e42–e51.
40. Xu XX, Li B, Yang HF, et al. Can diffusion-weighted imaging be used to differentiate brain abscess from other ring-enhancing brain lesions? A meta-analysis. *Clin Radiol*. 2014;69:909–915.

41. van de Beek D, Brouwer MC, Thwaites GE, et al. Advances in treatment of bacterial meningitis. *Lancet*. 2012;380:1693–1702.
42. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: A prospective multicenter observational study. *Clin Infect Dis*. 2007;44:250–255.
43. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64:701–706.
44. Wijdicks EFM, Zubkov AY. Principles of neurocritical care. In: Winn HR, ed. *Youmans Neurological Surgery*. 6th ed. Philadelphia: Saunders; 2011:429–437.
45. Molyneux EM, Walsh AL, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomized controlled trial. *Lancet*. 2002;360:211–218.
46. Smith M. Refractory intracranial hypertension: the role of decompressive craniectomy. *Anesth Analg*. 2017;125:1999–2008.
47. Ajdukiewicz KM, Cartwright KE, Scarborough M, et al. Glycerol adjunctive therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomized controlled trial. *Lancet Infect Dis*. 2011;11:293–300.
48. Mourvillier B, Tubach F, van de Beek D, et al. Induced hypothermia in severe bacterial meningitis: a randomized clinical trial. *JAMA*. 2013;310:2174–2183.
49. Lindvall P, Ahlm C, Ericsson M, et al. Reducing intracranial pressure may increase survival among patients with bacterial meningitis. *Clin Infect Dis*. 2004;38:384–390.
50. Oates-Whitehead R, Maconochie I, Baumer H, et al. Fluid therapy for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2005;(3):CD004786.

87 Acute Meningitis

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SHORT VIEW SUMMARY

Definition

- Meningitis, or inflammation of the meninges, is identified through an abnormal number of white blood cells in cerebrospinal fluid (CSF). Acute meningitis is clinically defined as a syndrome characterized by the onset of meningeal symptoms over the course of hours to up to several days.

Epidemiology

- Estimates from the Centers for Disease Control and Prevention (CDC) indicate that 10 to 15 million symptomatic enteroviral infections occur annually in the United States, which includes 30,000 to 75,000 cases of meningitis.
- In a surveillance study among residents in eight surveillance areas representing 17.4 million persons from 1998 to 2007, the impact of the heptavalent pneumococcal conjugate vaccine was appreciated, in which the incidence of bacterial meningitis caused by vaccine serotypes decreased from 0.61 cases per 100,000 population in 1998 to 1999 to 0.05 cases per 100,000 population in 2006 to 2007.
- In patients 16 years old or older, the relative frequency of isolation of meningeal pathogens in patients with community-acquired bacterial meningitis is somewhat different than in infants and children, with most cases caused by *Streptococcus pneumoniae, Neisseria meningitidis,* and *Listeria monocytogenes.*
- Sub-Saharan Africa has the highest incidence of meningitis due to epidemic meningococcal disease; in the past decade, serogroup A vaccine (MenAfriVac) has been successfully introduced in several countries and prevented new outbreaks.
- New epidemics of serogroup W and C meningococcal disease have occurred in sub-Saharan Africa, replacing serogroup A epidemics, whereas in European countries an increased incidence of cases caused by serogroup W has been described.

Microbiology

- Enteroviruses, currently the leading recognizable cause of aseptic meningitis syndrome, account for 85% to 95% of all cases in which a pathogen is identified.
- DNA of herpes simplex virus (HSV) has been detected in the CSF in published cases of Mollaret meningitis (now termed *recurrent benign lymphocytic meningitis*), almost all being HSV-2.
- A profound reduction has been seen in the incidence of invasive infections (including bacterial meningitis) caused by *Haemophilus influenzae* type b in the United States and western Europe; this decrease in infection is attributed, in part, to the widespread use of conjugate vaccines against *H. influenzae* type b that have been licensed for routine use in all children beginning at 2 months of age.
- From 1998 to 2007, a total of 2262 cases of meningococcal disease were reported to the Active Bacterial Core surveillance sites, with an annual incidence of 0.53 cases per 100,000 population; the incidence decreased from 0.92 cases per 100,000 population in 1998 to 0.33 cases per 100,000 population in 2007 before the introduction of the quadrivalent meningococcal conjugate vaccine.
- Patients with pneumococcal meningitis often have contiguous or distant foci of pneumococcal infection, such as pneumonia, otitis media, mastoiditis, sinusitis, and endocarditis; serious infection may be observed in patients with various underlying conditions (e.g., splenectomy or asplenic states, multiple myeloma, hypogammaglobulinemia, alcoholism, malnutrition, chronic liver or renal disease, malignancy, and diabetes mellitus).
- Outbreaks of *Listeria* infection have been associated with the consumption of contaminated coleslaw, raw vegetables, milk, and cheese, with sporadic cases traced to contaminated turkey franks, alfalfa tablets, cantaloupe, diced celery, hog head cheese (a meat jelly made from hog heads and feet), and processed meats, thus pointing to the intestinal tract as the usual portal of entry.
- Antibiotic prophylaxis has decreased neonatal early-onset disease caused by group B streptococci but with a concomitant rise in late-onset disease cases.
- Aerobic gram-negative bacilli (e.g., *Klebsiella* spp., *Escherichia coli, Serratia marcescens, Pseudomonas aeruginosa, Acinetobacter* spp., *Salmonella* spp.) have become increasingly important as etiologic agents in patients with bacterial meningitis; these agents may be isolated from the CSF of patients after head trauma or neurosurgical procedures and may also be found in neonates, older adults, immunosuppressed patients, and patients with gram-negative sepsis.

Diagnosis

- Nucleic acid amplification tests, such as polymerase chain reaction (PCR) assay, are the most promising alternatives to viral culture for the diagnosis of enteroviral meningitis.
- CSF culture is the gold standard in diagnosis of bacterial meningitis and is positive in 80% to 90% of patients with community-acquired disease if CSF is obtained before the start of antimicrobial therapy.
- Broad-based bacterial PCR can be used to detect the most common microorganisms of bacterial meningitis in only one test and has adequate sensitivity and excellent specificity. Such tests can be performed within 2 hours in most industrialized countries, but they are scarce in resource-poor countries.
- The diagnostic accuracy of CSF lactate is better than that of the CSF white blood cell count, glucose, and protein in the differentiation of bacterial from aseptic meningitis, with sensitivities of 93% and 97% and specificities of 96% and 94%.

Therapy

- The initial management of a patient with presumed bacterial meningitis includes performance of a lumbar puncture to determine whether the CSF formula is consistent with that diagnosis.
- If purulent meningitis is present, institution of antimicrobial therapy should be based on the results of Gram staining; however, if no etiologic agent can be identified by this means or if performance of the lumbar puncture is delayed, institution of empirical antimicrobial therapy should be based on the patient's age and underlying disease status.
- Certain patients with bacterial meningitis should also be treated with adjunctive dexamethasone. In a Cochrane Database systematic review of 24 studies involving 4041 participants, adjunctive dexamethasone did not reduce overall mortality, but there was a trend toward lower mortality in adults; corticosteroids were associated with lower rates of severe hearing loss, any hearing loss, and neurologic sequelae, although these benefits were seen only in studies from high-income countries.
- Penicillin can never be recommended as empirical therapy in patients with suspected pneumococcal meningitis; as an empirical regimen, the combination of vancomycin plus a third-generation cephalosporin (either

SHORT VIEW SUMMARY—cont'd

cefotaxime or ceftriaxone) is recommended, especially in countries with a ceftriaxone resistance rate >1%.
- Empirical treatment of gram-negative meningitis could begin with ceftazidime, cefepime, or meropenem. If the organism is later found to be resistant to these cephalosporins and the carbapenems, colistin (usually formulated as colistimethate sodium) or polymyxin B should be substituted for meropenem and may also need to be administered by the intraventricular or intrathecal route.

Prevention

- Chemoprophylaxis is necessary for close contacts of patients with invasive meningococcal disease; the CDC currently recommends the administration of rifampin, ciprofloxacin, or ceftriaxone, which are all 90% to 95% effective at eradicating nasopharyngeal carriage, although cases of ciprofloxacin-resistant *N. meningitidis* have been reported in North Dakota and Minnesota, leading the CDC to no longer recommend ciprofloxacin for meningococcal chemoprophylaxis in selected counties of these states.
- Vaccination to prevent infection with specific meningeal pathogens is a very useful measure for decreasing the incidence of bacterial meningitis.
- For *H. influenzae* type b, the availability of conjugate vaccines has decreased the number of cases of *H. influenzae* type b meningitis by more than 90%.
- The first meningococcal conjugate vaccine (meningococcal polysaccharide-diphtheria toxoid conjugate vaccine containing serogroups A, C, W, and Y polysaccharides) was licensed for use in the United States for routine vaccination of all persons aged 11 to 18 years with one dose. In updated guidelines, a booster dose is now recommended at age 16 years and a two-dose primary series is administered 2 months apart for persons aged 2 through 54 years with persistent complement component deficiency or functional or anatomic asplenia and for adolescents with human immunodeficiency virus infection. Other persons who are at risk for meningococcal disease (e.g., microbiologists or travelers to an epidemic or highly endemic country) should receive a single dose. Two protein vaccines are marketed for short term protection against serogroup B menngococcal infection.
- The Advisory Committee on Immunization Practices now recommends use of the 13-valent pneumococcal conjugate vaccine to prevent pneumococcal disease in infants and children aged younger than 6 years; this vaccine has activity against the serotypes that were present in the heptavalent vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) along with six additional serotypes (1, 3, 5, 6A, 7F, and 19A).

DEFINING ACUTE MENINGITIS

Meningitis, or inflammation of the meninges, is typically identified by means of a cerebrospinal fluid (CSF) pleocytosis of more than five white blood cells (WBCs) in the CSF, even though approximately up to 8% of patients with central nervous system (CNS) infections can present with absence of CSF pleocytosis.[1] Acute meningitis (duration of symptoms of less than 5 days) accounts for 75% of all community-acquired meningitis cases and is most commonly caused by unknown pathogens, as well as viral and bacterial organisms.[2] In contrast, patients with subacute meningitis (duration of 5 days or more) are more likely to have comorbidities, be immunosuppressed, have fungal etiologies, or present with abnormal neurologic examination findings or with hypoglycorrhachia (CSF glucose <45 mg/dL).[2] It is very important to distinguish acute or subacute meningitis syndromes from chronic meningitis (see Chapter 88) and encephalitis (see Chapter 89). Chronic meningitis (>4 weeks' duration of symptoms and signs and CSF abnormalities) has a broad differential diagnosis that includes conditions such as fungal infection, mycobacterial infection, neurobrucellosis, neurosyphilis, sarcoidosis, autoimmune disorders, paraneoplastic disorders, and vasculitis.[3] Encephalitis is a community-acquired illness with altered mental status for more than 24 hours with at least two (possible encephalitis) or three (probable encephalitis) of the following criteria: fever, new-onset seizure, new-onset focal neurologic finding, CSF pleocytosis, and abnormal findings at magnetic resonance imaging (MRI) of the brain or electroencephalogram (EEG) consistent with encephalitis.[4] The distinction among all of these syndromes is clinically useful in guiding management, but there can be significant overlap among the different causes; for example, West Nile virus (WNV) and herpes simplex virus (HSV) can lead to either an acute meningitis or an encephalitis presentation.

The acute meningitis syndrome may arise from a wide variety of infectious and noninfectious causes (Table 87.1). Diseases in which meningeal symptoms occur but are not predominant are excluded from the table. Many of the causes of chronic meningitis, which can manifest acutely, have been omitted but are listed in Chapter 88. Here, we review the common infectious causes of acute meningitis, with particular emphasis on epidemiology and etiology, pathogenesis and pathophysiology, clinical manifestations, diagnosis, management, and prevention.

EPIDEMIOLOGY AND ETIOLOGY

Viral Meningitis

Viruses are the most commonly identified cause of the *aseptic meningitis syndrome,* a term used for a community-acquired illness with CSF pleocytosis, a negative CSF or blood culture, normal neurologic examination findings, and a benign clinical outcome.[5] The most common viral etiologic agents that cause the acute aseptic meningitis syndrome are enteroviruses (EVs), herpesviruses, and arboviruses such as WNV.[5] These and other less common viruses are discussed in the following paragraphs.

Enteroviruses

EVs are currently the leading recognizable cause of aseptic meningitis syndrome, accounting for 48% to 95% of all cases in which a causative virus is identified.[5–7] Enteroviral infections are underreported to the Centers for Disease Control and Prevention (CDC) because surveillance is passive and because enteroviral infections are underdiagnosed, especially in adults, in whom a CSF EV polymerase chain reaction (PCR) assay is performed in only 15%.[5–7] A total of 118 types of EVs and 16 types of human parechoviruses (HPeVs) (both small viruses of the Picornaviridae family) have been described as causes of viral meningitis in the United States.[7] In addition to aseptic meningitis, these viruses can sometimes also cause acute flaccid paralysis (AFP), encephalitis, myocarditis, and sepsis, with worse clinical presentations most commonly seen in neonates or infants.[7] EVs have a worldwide distribution and, in temperate climates, have a summer/fall seasonality, although in tropical and subtropical areas they can occur perenially.[6] Transmission is mainly via the fecal-oral route, but it has also been documented via respiratory droplets.[6] From 2009 to 2013, based on data from the CDC laboratory-based surveillance system (the National Enterovirus Surveillance System), the majority of cases occurred from April to November and the two most common viruses identified were coxsackievirus A6, and HPeV type 3, accounting for a total of 24.6% of total serotypes detected.[7] Recently, EV D68 was implicated as a possible cause of AFP in the United States, as 43% of cases had EV D68 isolated from respiratory specimens with PCR.[8] A total of 202 cases of AFP (patients' median age ranging between 9 and 11 years) were described in the United States from 2012 to 2015, with the majority of patients having neurologic deficits at 1-year follow-up. In addition, EV 71 can also cause AFP, in addition to aseptic meningitis and a brainstem encephalitis, which may manifest with shock and pulmonary edema.[9] EV 71 has been implicated in large cyclic epidemics in Southeast Asia, but cases have now been reported worldwide.[10,11] From 2005 to 2008, EV 71 was detected in 29 patients in Denmark,[11] with the majority of them presenting with meningitis. Outbreaks of enteroviral meningitis have also been reported.[12–15] One outbreak involved 29 travelers in a school-organized trip to Mexico[12]; most cases were caused by echovirus 30 and coxsackievirus A1. Other reported enteroviral meningitis outbreaks have

TABLE 87.1 Differential Diagnosis of Acute Meningitis

Major Infectious Causes

Viruses

Nonpolio enteroviruses[a]
Arboviruses[b]
Herpesviruses[c]
Lymphocytic choriomeningitis virus
Human immunodeficiency virus
Adenovirus
Parainfluenza virus types 2 and 3

Rickettsiae

Rickettsia rickettsii
Rickettsia conorii
Rickettsia prowazekii
Rickettsia typhi
Orientia tsutsugamushi
Ehrlichia and *Anaplasma* spp.

Bacteria

Haemophilus influenzae
Neisseria meningitidis
Streptococcus pneumoniae
Listeria monocytogenes
Escherichia coli
Streptococcus agalactiae
Cutibacterium (formerly *Propionibacterium*) *acnes*
Staphylococcus aureus
Staphylococcus epidermidis
Enterococcus spp.
Klebsiella pneumoniae
Pseudomonas aeruginosa
Salmonella spp.
Acinetobacter spp.
Viridans streptococci (e.g., *Streptococcus salivarius*)
Streptococcus gallolyticus
Fusobacterium necrophorum
Stenotrophomonas maltophilia
Streptococcus pyogenes
Streptococcus suis
Pasteurella multocida
Capnocytophaga canimorsus
Nocardia spp.
Mycobacterium tuberculosis

Spirochetes

Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme disease)
Borrelia miyamotoi
Leptospira spp.

Protozoa and Helminths

Naegleria fowleri
Angiostrongylus cantonensis
Baylisascaris procyonis
Taenia solium
Toxocara spp.
Strongyloides stercoralis (hyperinfection syndrome)

Other Infectious Syndromes

Parameningeal foci of infection[d]
Infective endocarditis
Viral postinfectious syndromes
Postvaccination[e]

Noninfectious Causes and Diseases of Unknown Etiology

Intracranial Tumors and Cysts

Craniopharyngioma
Dermoid or epidermoid cyst
Teratoma

Medications

Antimicrobial agents[f]
Nonsteroidal antiinflammatory agents[g]
Muromonab-CD3 (OKT3)
Azathioprine
Cytarabine (high dose)
Carbamazepine[h]
Immune globulin
Ranitidine
Phenazopyridine

Systemic Illnesses

Systemic lupus erythematosus
Behçet disease
Sarcoidosis
Vogt-Koyanagi-Harada syndrome

Procedure Related

After neurosurgery
Spinal anesthesia
Intrathecal injections[i]
Chymopapain injection

Miscellaneous

Seizures
Migraine or migraine-like syndromes

[a]Primarily echoviruses and coxsackieviruses.
[b]In the United States, the major etiologic agents are the mosquito-borne California, St. Louis, eastern equine, and West Nile viruses and the tick-borne Colorado tick fever.
[c]Primarily herpes simplex virus type 2 but also herpes simplex virus type 1, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6.
[d]Brain abscess, sinusitis, otitis, mastoiditis, subdural empyema, epidural abscess, venous sinus thrombophlebitis, pituitary abscess, cranial osteomyelitis.
[e]Mumps, measles, polio, pertussis, rabies, vaccinia.
[f]Trimethoprim, sulfamethoxazole, trimethoprim-sulfamethoxazole, ciprofloxacin, penicillin, isoniazid, metronidazole, cephalosporins, pyrazinamide.
[g]Ibuprofen, sulindac, naproxen, tolmetin, diclofenac, ketoprofen.
[h]In patients with connective tissue diseases.
[i]Air, isotopes, antimicrobial agents, antineoplastic agents, corticosteroids, radiographic contrast media.

been caused by coxsackievirus B3[13] and echovirus types 18 and 30.[14,15]

Infants and young children are the primary victims of enteroviral meningitis because they are the most susceptible host population within the community. In a study of 156 enteroviral infections in children, risk factors for severe disease were absence of oral lesions, seizures, and lethargy, with the majority of the severe cases caused by EV 71 and coxsackievirus A16.[16] EVs are also a common cause of aseptic meningitis in adults, but these patients invariably have good clinical outcomes.[5] A few cases of enteroviral meningoencephalitis have also been seen in patients treated with the chimeric anti-CD20 monoclonal antibody rituximab.[17,18]

Herpesviruses

Herpesviruses include HSV types 1 and 2, varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus (HHV) types 6, 7, and 8. Although neurologic complications are known to occur with some of these viruses, complications associated with HSV are of the greatest significance. In a study of 404 adults with aseptic meningitis, HSV was the most commonly identified viral pathogen even though only 39% of patients had a CSF HSV PCR assay performed.[5] In patients beyond the neonatal period, it is critical to differentiate between HSV encephalitis (usually caused by HSV type 1), a potentially fatal infection, and HSV meningitis (most commonly caused by HSV type 2), a self-limited syndrome. The syndrome of HSV-2 aseptic meningitis is most commonly associated with primary genital infection and has a benign clinical outcome that does not appear to be impacted by antiviral therapy.[19] HSV-2 is also the most common cause of Mollaret meningitis (now termed *recurrent benign lymphocytic meningitis*), although a few cases associated with HSV-1 and EBV have been reported.[20] The majority of patients are female, have no history of genital HSV, and have no active lesions at presentation.[20] A double-blind,

randomized clinical trial of valacyclovir suppression showed no impact on decreasing recurrent rates in patients with HSV-2 meningitis.[21] Acute aseptic meningitis has also been associated with VZV in patients with or without typical skin lesions,[19] the latter known as *zoster sine herpete.* VZV is most likely an underdiagnosed treatable cause, because only 1.2% of patients with aseptic meningitis undergo a CSF VZV PCR assay.[5] A study in which a multiplex PCR assay was used documented that HHV-6 was more commonly detected than HSV-1 or HSV-2 in adults and children with meningitis and encephalitis.[22] The proportion of these HHV-6 cases that represent a true infection, versus reactivation or chromosomal integration, remains to be determined.[23] CMV and EBV may cause aseptic meningitis in association with a mononucleosis syndrome, particularly in an immunocompetent host.[24]

Arboviruses

Arboviruses (*ar*thropod-*bo*rne virus) include several families of viruses that are transmitted by mosquitos, ticks or sand flies.[25] The most common arthropod-transmitted cause of aseptic meningitis in the United States is WNV, a flavivirus. WNV infection is most commonly asymptomatic, with approximately 20% of patients having a febrile illness and 1% presenting with neuroinvasive disease.[26] Neuroinvasive disease may present as an aseptic meningitis, encephalitis or an AFP/myelitis, but may be underdiagnosed because only approximately one-third of adults and children with meningitis or encephalitis are tested.[27] There is no vaccine or therapy for WNV infection.

Less common arboviruses in the United States that can cause aseptic meningitis are two mosquito-borne illnesses—St. Louis encephalitis (a flavivirus) and the California encephalitis group of viruses (e.g., La Crosse, Jamestown Canyon, and snowshoe hare viruses, which are bunyaviruses)—and two tick-borne illnesses—Powassan virus in the northern central and eastern United States, and coltivirus (agent of Colorado tick fever) in the mountainous and western regions of the United States and Canada.[25] In 2015 the CDC reported a total of 2175 cases of WNV, followed by La Crosse (55), St. Louis encephalitis (23), Jamestown Canyon (11), Powassan (7), and eastern equine encephalitis (6).[28] In Europe, tick-borne encephalitis can be associated with a complex syndrome of meningoencephaloradiculitis (MER), which is associated with a relatively high risk of severe disease (requirement for intensive care and mechanical ventilation). Age, male sex, and preexisting diabetes mellitus were predictive of the more severe MER.[29] Toscana virus has emerged as one of the most common causes of meningitis or encephalitis during the summer in the Mediterranean countries[30]; it is transmitted by sand flies and is a bunyavirus.

Other Viruses

Lymphocytic choriomeningitis virus (LCMV) can cause aseptic meningitis[24]; this virus is now rarely reported as an etiologic agent.[5] A seroprevalence of 5% for LCMV was seen in 400 patients with neurologic infections, but there were no documented cases by PCR assay.[31] LCMV is transmitted to humans by contact with rodents (e.g., hamsters, rats, mice) or their excreta[24]; the greatest risk for infection is in laboratory workers, pet owners, and persons living in impoverished and unhygienic situations. Recent outbreaks have been reported in rodent breeding factories or infected households.[32,33] No evidence of human-to-human transmission has been reported.

In an unimmunized population, mumps can cause aseptic meningitis and encephalitis.[24] With the introduction of the measles-mumps-rubella (MMR) vaccine, the incidence of mumps-associated meningitis has dramatically decreased, now accounting for <1% of all cases of meningitis and encephalitis in the United Kingdom and the United States.[34,35]

Human immunodeficiency virus (HIV) can cause aseptic meningitis during HIV seroconversion; the clinical presentation is a mononucleosis-like picture.[24] HIV may also cause an encephalitis presentation in those with acquired immunodeficiency syndrome (AIDS) who are not receiving antiretroviral therapy (ART) (known as AIDS encephalopathy or HIV encephalitis) or in those patients on ART with CSF viral escape (detectable viral load in the CSF with undetectable or low-level viremia).[36] This latter form is named CD8 encephalitis and can be treated with steroids and by optimizing ART. A recent large study of community-acquired meningitis in the United States showed that 25% of patients tested had HIV coinfection.[37]

Japanese encephalitis is a vaccine-preventable infection that continues to cause both meningitis and encephalitis in countries where routine vaccination is not available.[38] Dengue, chikungunya, and Zika viruses are emerging causes of meningitis or encephalitis in several parts of the world.[39,40] The epidemic of Ebola virus disease in West Africa has revealed unusual characteristics of the disease not previously described, including viral relapse with acute meningitis, with high concentrations of virus in CSF. Antiviral therapy with an experimental agent and adjuvant corticosteroids led to resolution of the disease.[41] Other newly identified causes of meningitis include astrovirus MLB2, usually a gastrointestinal virus, and Cache Valley virus in an immunosuppressed individual.[42,43]

Bacterial Meningitis

Overview of Bacterial Meningitis

Bacterial meningitis is an important disease worldwide, with the major burden of disease in sub-Saharan Africa.[44,45] The Global Burden of Disease Study showed that meningitis caused 318,000 deaths each year worldwide (4.5 per 100,000 persons), resulting in 20,383 years of life lost in 2016.[46] The incidence rates vary per country, with most recent rates varying from 0.7 to 0.9 per 100,000 per year in the United States and European countries, whereas studies from Africa describe incidence rates varying from 10 to 40 per 100,000 per year.[47]

Studies on the epidemiology of community-acquired bacterial meningitis in the United Status showed that the disease changed substantially over the past 40 years (Table 87.2).[48–51] The overall annual attack rate for bacterial meningitis identified in a surveillance study of 27 states in the United States from 1978 through 1981 was approximately 3.0 cases per 100,000 population, with variability based on age, race, and sex.[48] The three most common meningeal pathogens were shown to be *Haemophilus influenzae, Neisseria meningitidis,* and *Streptococcus pneumoniae,* accounting for more than 80% of cases. A 1995 laboratory surveillance study serving acute-care hospitals in 22 counties of four states (>10 million population) showed that the incidence of bacterial meningitis decreased dramatically.[50] This decrease was a result of a vaccine-related decline in meningitis caused by *H. influenzae* type b

TABLE 87.2 Etiology of Bacterial Meningitis in the United States

	PERCENTAGE OF TOTAL CASES			
ORGANISM	**1978–1981[39]**	**1986[40]**	**1995[41]**	**2003–2007[42]**
Haemophilus influenzae	48	45	7	7
Neisseria meningitidis	20	14	25	14
Streptococcus pneumoniae	13	18	47	58
Streptococcus agalactiae	3	6	12	18
Listeria monocytogenes	2	3	8	3
Other	8	14	—	—
Unknown	6	—	—	—

(from 2.9 cases per 100,000 population in 1986 to 0.2 cases per 100,000 population in 1995).[49,50] In another surveillance study among residents in eight surveillance areas representing 17.4 million persons from 1998 to 2007, the impact of the heptavalent pneumococcal conjugate vaccine was appreciated; the incidence of meningitis caused by vaccine serotypes decreased from 0.61 cases per 100,000 population in 1998 to 1999 to 0.05 cases per 100,000 population in 2006 to 2007, although the number of cases of bacterial meningitis caused by nonvaccine serotypes increased by 61%.[50] The mean age of all patients with meningitis increased from 30.3 years in 1998 to 1999 to 41.9 years in 2006 to 2007. However, despite the declining incidence of bacterial meningitis in the United States, the overall case-fatality rates did not change significantly (15.7% in 1998 to 1999 compared with 14.3% in 2006 to 2007; $P = .50$).

Epidemiology of bacterial meningitis differs according to age group, with higher incidences in the very young (neonates) and the elderly.[52] In neonates, the majority of meningitis cases are caused by *Streptococcus agalactiae* (or group B streptococci) and *Escherichia coli*.[53] Whereas *Listeria monocytogenes* has traditionally been considered an important pathogen in neonates, 21st century epidemiologic studies from the United Kingdom and the Netherlands show that it is now an uncommon pathogen.[54,55] In children beyond the neonatal age, *S. pneumoniae* and *N. meningitidis* cause up to 90% of cases (Table 87.3).

In patients 16 years old or older, most cases are caused by *S. pneumoniae, N. meningitidis,* and *L. monocytogenes* (see Table 87.3).[47–51] Risk factors for meningitis in adults consist of splenectomy or splenic dysfunction, alcoholism, HIV, diabetes, cancer, use of immunosuppressive medications, solid organ transplantation, and bone marrow transplantation.[56–59] In selected groups, the increased risk of infection should warrant additional vaccination—for instance, in patients with splenectomy. Elderly patients and patients in an immunocompromised state are at higher risk of *L. monocytogenes* meningitis, which should therefore be covered in the empirical antibiotic treatment in anyone older than 50 years and in those in an immunocompromised state, irrespective of age.[52,53] Risk factors for death on admission among adults with community-acquired meningitis include older age, absence of otitis or sinusitis, alcoholism, tachycardia, lower score on the Glasgow Coma Scale, cranial nerve palsy, a CSF WBC count of less than 1000 cells per microliter, a positive blood culture, and a high serum C-reactive protein (CRP) concentration.[60]

Geographic differences in bacterial meningitis epidemiology are substantial (Table 87.4).[50–53] The majority of cases worldwide occur in sub-Saharan Africa, a region often referred to as the "meningitis belt." Epidemic meningococcal disease causes peaks in meningococcal meningitis incidence up to 100 per 100,000 population.[61] A study from Burkina Faso showed that despite the epidemics of meningococcal disease, 53% of cases were caused by *S. pneumoniae*.[62] In regions with high rates of HIV infection, bacterial meningitis due to nontyphoidal *Salmonella* species causes a substantial proportion of cases.[63,64] In Southeast Asia, the most common pathogen is *Streptococcus suis*, which is found in 25% to 30% of cases[65]; risk factors are close contact with pigs due to pig farming or the pork-processing industry, and alcoholism.[66]

Outcome also differs geographically, with mortality rates ranging from 54% in Malawi to 6% in Germany.[67,68] Mortality from neonatal meningitis in developing countries is estimated to be 40% to 58%, compared with only 10% in the developed world.[69]

Meningitis acquired in the hospital, whether after neurosurgical intervention, due to neurosurgical implants (e.g., CSF drains, deep brain stimulators), or during admission for other diseases, is also a significant problem. A 2017 guideline by the Infectious Diseases Society of America (IDSA) renamed this as *health care–associated ventriculitis and meningitis,* replacing the previously used term *nosocomial meningitis.*[70] In a review of 493 episodes of bacterial meningitis in adults 16 years old or older at the Massachusetts General Hospital from 1962 through 1988, 40% of episodes were found to be health care associated, with most cases (38%) caused by gram-negative bacilli.[71] The overall case-fatality rate for patients with health care–associated meningitis was 35% and did not vary significantly over the 27 years of the study. In a 2012 study from Korea of 91 adult patients with health care–associated meningitis, coagulase-negative staphylococci (41% of cases) and *Acinetobacter* species (33% of cases) were the most common pathogens, with 86% of patients having infection related to an external ventricular drain.[72] More recently

TABLE 87.3 Etiology of Bacterial Meningitis in Patients 16 Years of Age and Older

	PERCENTAGE OF TOTAL CASES			
ORGANISM	UNITED STATES (1962–1988)[44]	ICELAND (1975–1994)[43]	CANADA (1985–1995)[45]	UNITED STATES (1970–1998)[46]
Haemophilus influenzae	4	5	8	4
Neisseria meningitidis	14	56	2	14
Streptococcus pneumoniae	38	20	53	48
Listeria monocytogenes	11	6	25	7
Other[a]	20	—	12	27
Unknown	13	8	—	—

[a]Includes gram-negative bacilli, streptococci, enterococci, *Staphylococcus aureus,* anaerobes, and diphtheroids.

TABLE 87.4 Etiology of Bacterial Meningitis in Selected Series Outside the United States

	PERCENTAGE OF TOTAL CASES			
ORGANISM	UNITED KINGDOM (1980–1984)[50]	DAKAR, SENEGAL (1970–1979)[51]	SALVADOR, BRAZIL (1973–1982)[52]	MEXICO (1993–2003)[53]
Haemophilus influenzae	29	20	23	50
Neisseria meningitidis	25	11	22	2
Streptococcus pneumoniae	20	29	27	31
Streptococcus agalactiae	7	4	—	—
Listeria monocytogenes	2	<0.5	—	—
Other	16	9	20	6
Unknown	—	26	18	11

in 2016, a study of 215 adults and children with health care–associated meningitis demonstrated that 78% had adverse clinical outcomes; significant predictors were age >45 years, abnormal neurologic examination findings, and mechanical ventilation.[73]

In patients who survive their episode of bacterial meningitis, significant sequelae have been reported, with the risks for long-term disabling sequelae highest in low-income countries where the burden of bacterial meningitis is greatest. In a review of 132 studies including 18,183 survivors of acute bacterial meningitis, the risk for a major sequela (cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus) was greatest in Africa (25.1%) and southeast Asia (21.6%) when compared with Europe (9.4%)[74]; the risk for at least one major sequela was also pathogen dependent—24.7% in survivors of pneumococcal meningitis compared with 9.5% with *H. influenzae* type b meningitis and 7.2% with *N. meningitidis* meningitis. In another literature review of 1433 children who were survivors of bacterial meningitis, 705 were reported to have one or more long-term sequelae, the majority of which were behavioral or intellectual disorders or both.[75] In a prospective study, cognitive impairment was noted in 32% of adults after bacterial meningitis and mainly consisted of cognitive slowness.[76]

The likely etiologic agents of bacterial meningitis vary according to the age and underlying disease status of the patient (Table 87.5). The epidemiology and etiology of specific meningeal pathogens are reviewed next.

Haemophilus influenzae

H. influenzae was isolated in 45% to 48% of all cases of bacterial meningitis in the United States before introduction of the *H. influenzae* type b vaccine[48,49]; this organism is now isolated in only 3% to 7% of cases.[50,51,60] The overall mortality rate is 3% to 7%.[48–51,77] Most episodes of meningitis previously occurred in infants and children younger than 6 years (peak incidence of 6 to 12 months), with 90% of cases caused by capsular type b strains. Isolation of this organism in older children and adults should suggest the presence of certain underlying conditions, including sinusitis, otitis media, epiglottitis, pneumonia, diabetes mellitus, alcoholism, splenectomy or asplenic states, head trauma with CSF leak, and immune deficiency (e.g., hypogammaglobulinemia).[77–80] A profound reduction has been seen in the incidence of invasive infections (including bacterial meningitis) caused by *H. influenzae* type b in the United States and western Europe.[81–84] This decrease in infection is mainly attributed to the widespread use of conjugate vaccines against *H. influenzae* type b that have been licensed for routine use in all children beginning at 2 months of age. The number of cases of *H. influenzae* type b meningitis since the introduction of vaccination has decreased more than 90%, although because of vaccine expense, in developing countries the results are not as dramatic. Although the incidence in children has dramatically declined, the incidence of invasive *H. influenzae* disease in adults is more complex. In one population-based study of the epidemiology and outcome caused by typeable and nontypeable *H. influenzae* among adults in Utah during 1998 to 2008, there was an increase in incidence over the study period from 0.14 per 100,000 person-years in 1998 to 1.61 per 100,000 person-years in 2008 (subjects >65 years of age accounted for 51% of the cases and 67% of the deaths).[85]

TABLE 87.5 Relationship Between Common Bacterial Pathogens and Factors Predisposing to Meningitis

PREDISPOSING FACTOR	BACTERIAL PATHOGENS
Age	
<1 mo	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes*
1–23 mo	*S. agalactiae, E. coli, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*
2–50 yr	*S. pneumoniae, N. meningitidis*
>50 yr	*S. pneumoniae, N. meningitidis, L. monocytogenes*, aerobic gram-negative bacilli
Immunocompromised state	*S. pneumoniae, N. meningitidis, L. monocytogenes*, aerobic gram-negative bacilli (including *Pseudomonas aeruginosa)*
Basilar skull fracture	*S. pneumoniae; H. influenzae;* group A streptococci
Head trauma; after neurosurgery	*Staphylococcus aureus*, coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *P. aeruginosa*)

Neisseria meningitidis

N. meningitidis most commonly causes meningitis in children and young adults and is associated with an overall mortality rate of 3% to 13% in the United States.[48–51] More than 98% of cases of invasive meningococcal disease are sporadic.[86] Meningococci of serogroups B, C, and Y account for most of the endemic disease in the United States; disease caused by serogroups A and W seldom occurs in the United States. Annual outbreaks of meningococcal meningitis occur in the sub-Saharan meningitis belt during the dry season (December to June); cases tend to peak in late April and early May, when the dry desert wind (harmattan) has ceased and temperatures are high throughout the day, and terminate abruptly with the onset of the rainy season. During an active and ongoing, laboratory-based, population-based surveillance for meningococcal disease in the United States from 1992 to 1996, serogroup C caused 35%, serogroup B caused 32%, and serogroup Y caused 26% of cases.[87] Disease caused by serogroups A and C may occur in epidemics; group Y strains may be associated with pneumonia. From 1998 to 2007, a total of 2262 cases of meningococcal disease were reported to the Active Bacterial Core surveillance sites, with an annual incidence of 0.53 cases per 100,000 population.[51] The incidence decreased from 0.92 case per 100,000 population in 1998 to 0.33 cases per 100,000 population in 2007, with this historic low occurring before the introduction of the quadrivalent meningococcal conjugate vaccine. Infants younger than 1 year of age had the highest incidence (5.38 cases per 100,000 population), although the distribution of serogroups is also different in this population (serogroup B, 3.08 per 100,000 population; serogroup C, 0.53 per 100,000 population; and serogroup Y, 1.50 per 100,000 population). During the outbreak of meningococcal disease coinciding with the Hajj pilgrimage in March 2000, the attack rate of serogroup W disease was 25 cases per 100,000 pilgrims[88]; all outbreak-associated isolates of serogroup W were members of a single clone of the hypervirulent ET-37 complex, which occurred as the result of expansion of a clone that had been in circulation since 1970.[89] A high incidence of serogroup X cases was reported in Niger,[90] representing 51% of 1139 confirmed cases of meningococcal meningitis in 2006; serogroup X disease also emerged in Togo and Burkina Faso during 2006 to 2010.[91] A tenfold increase in incidence of serogroup W meningococcal disease was observed in the Netherlands after 2015, which was similar to a hyperendemic period of serogroup W disease in the United Kingdom occurring after 2009.[92,93] After replacement of the serogroup C vaccine with the ACWY vaccine in the United Kingdom, the incidence decreased by 69%.[94] Since 2010, large-scale vaccination campaigns against serogroup A meningococci have started in sub-Saharan Africa, resulting in a sharp decrease in epidemic meningococcal meningitis.[95] This almost completely prevented serogroup A disease and reduced the incidence of meningococcal disease by 57%.[95] However, since 2015, epidemics of serogroup C meningococcal have replaced those caused by serogroup A, with comparable incidence rates as were observed before vaccination. Continuous surveillance and quickly adaptable vaccination strategies are of vital importance to counter these epidemics.

A 2017 study of surveillance data from 25 European countries assessed almost 50,000 cases of meningococcal disease from the period of 2004 to 2014 and showed a variable incidence, ranging from 0.3 to 2.9 cases per 100 000 per year.[96] Overall, 74% of cases were caused by serogroup B, and serogroup C was the second most common, identified in 14% of cases.[96] In countries in which the serogroup C meningococcal conjugate vaccine (MenC) was implemented, a sharp decrease in serogroup C meningococcal disease was observed, whereas the incidence remained

similar in countries in which the vaccine was not introduced. An 8% annual decrease of serogroup B meningococcal disease was observed over the observation period, even though no vaccination had been introduced.

Respiratory tract infections, with viruses such as influenza virus, may play a role in the pathogenesis of invasive meningococcal disease.[79] Nasopharyngeal carriage of *N. meningitidis* is an important factor that leads to the development of invasive disease.[80] Patients with deficiencies in the terminal complement components (C5, C6, C7, C8, and perhaps C9), the so-called membrane attack complex, have a markedly increased incidence of neisserial infection,[81–83] including that caused by *N. meningitidis,* although mortality rates in patients with meningococcal disease are lower than those in patients with an intact complement system (3% vs. 19% in the general population). An increased risk for invasive meningococcal disease has also been described in a Dutch family with dysfunctional properdin,[84] which suggests a potential role for the alternate pathway in complement-mediated resistance against meningococci. Because meningococcal meningitis occurs in approximately 39% of persons with late complement component deficiencies and 6% of those with properdin deficiencies, it has been suggested that a screening test for complement function (i.e., CH_{50}) should be performed for patients who have invasive meningococcal infections, with consideration of direct assessment of terminal complement components and properdin proteins.[85] However, this is most appropriate for patients with recurrent neisserial infections. It has also been recently reported that unusual meningococcal strains with low levels of virulence similar to carriage strains are most frequently responsible for invasive meningococcal disease in patients with terminal complement pathway deficiency.[97] In addition, there is an increased risk of having meningococcal disease in men who have sex with men (MSM); the relative risk (RR) is 4 in MSM, and 10 if they are also HIV infected.[98] Most recently, there has been an increased risk in patients who are receiving eculizumab (1000- to 2000-fold increased risk).[99]

A vaccine for serogroup B meningococcal disease has been developed and was shown to be immunogenic in a randomized controlled trial.[100] After introduction of the vaccine in the United Kingdom in 2015, an incidence reduction of 50% was observed.[101] Based on the meningococcal typing system, it was predicted that two-thirds of serogroup B meningococci in the United Kingdom are covered by the vaccine, with rates varying between 60% and 80% in other European countries.[102,103]

Streptococcus pneumoniae

S. pneumoniae, the most frequently observed etiologic agent of bacterial meningitis in the United States, now accounts for 58% of the total cases.[51] Epidemiologic changes have been observed since introduction of the 7-valent pneumococcal conjugate vaccine (PCV7).[104] The incidence of pneumococcal meningitis decreased in children first, and later also in adults. The decrease was the result of a reduction of cases due to serotypes included in the vaccine, but at the same time an increased incidence in nonvaccine serotypes occurred, limiting the effect of the vaccine's introduction.[104] After this increase, vaccines covering additional serotypes (PCV10 and PCV13) have replaced PCV7. A 2016 study from France assessing 5166 pneumococcal isolates from meningitis cases showed that the effect of the introduction of PCV7 and PCV13 was modest.[47,105] In Ghana, introduction of PCV13 did not prevent a serotype 1 outbreak in 2015 and 2016, with incidence rates of 363 per 100,000 persons.[106] Overall a modest reduction in incidence of pneumococcal meningitis has been observed with frequent serotype replacement. In invasive pneumococcal disease other than meningitis, the effect of vaccination was substantially better, which was explained by different tropism for the meninges of the serotypes.[107]

The mortality rate of pneumococcal meningitis ranges from 18% to 26% in the United States.[48–51] In one study of 352 episodes of community-acquired pneumococcal meningitis in adults, 245 (70%) were associated with an underlying disorder and the overall in-hospital mortality rate was 30%[108]; independent predictors of unfavorable outcome were a low score on the Glasgow Coma Scale, cranial nerve palsies, elevated erythrocyte sedimentation rate, a CSF WBC count of less than 1000/mm,[3] and a high CSF protein concentration on admission. There was a high rate of neurologic sequelae in survivors; death in patients younger than 60 years was more often caused by neurologic complications, and in patients 60 years or older it was more likely secondary to systemic complications. Of the more than 90 known pneumococcal serotypes, 18 are responsible for 82% of the cases of bacteremic pneumococcal pneumonia, with a close correlation between bacteremic subtypes and those implicated in meningitis. Patients often have contiguous or distant foci of pneumococcal infection, such as pneumonia, otitis media, mastoiditis, sinusitis, and endocarditis. Serious infection may be observed in patients with various underlying conditions (e.g., splenectomy or asplenic states, multiple myeloma, hypogammaglobulinemia, alcoholism, HIV chronic liver or renal disease, malignancy, and diabetes mellitus).[109–112] Remote head injury and CSF leak are important predisposing factors for recurrent bacterial meningitis.[113] The pneumococcus is the most common etiologic agent of meningitis in patients who have sustained a basilar skull fracture with CSF leak.[114]

Listeria monocytogenes

L. monocytogenes causes 2% to 8% of cases of bacterial meningitis in the United States and carries a mortality rate of 15% to 29%.[48–51] Serotypes 1/2b and 4b have been implicated in up to 80% of meningitis cases caused by this organism. Epidemiologic data show that the incidence of *L. monocytogenes* meningitis is highest in neonates and elderly, with incidences up to 0.61 per 100,000 in neonates and 0.53 per 100,000 in the elderly.[54] A study from the Netherlands showed that the incidence of neonatal *Listeria* meningitis had decreased in the previous 25 years, potentially because of increased awareness of food restrictions for pregnant women. The rate of unfavorable outcome among adults with *Listeria* meningitis was found to increase over a 14-year period from 27% to 61%, with the emerging *L. monocytogenes* sequence type 6 identified as the main factor leading to a poorer prognosis.[115] A follow-up whole-genome sequencing study of these *Listeria* strains identified a plasmid containing the benzalkonium chloride tolerance gene that was associated with decreased susceptibility to disinfectants commonly used in the food-processing industry. Strains containing the plasmid had increased minimal inhibitory concentrations (MICs) to amoxicillin and gentamicin, which are commonly used in treatment of *L. monocytogenes* infections.[116]

Listeria has been isolated from dust, soil, water, sewage, and decaying vegetable matter (including animal feed and silage). Listerial infection is most common in infants younger than 1 month (up to 10% of cases), adults older than 60 years, alcoholics, cancer patients, those receiving corticosteroid therapy, and immunosuppressed adults (e.g., renal transplant recipients).[117–119] Other predisposing conditions include diabetes mellitus, liver disease, chronic renal disease, collagen vascular diseases, pregnancy, and conditions associated with iron overload. Although colonization rates are low, pregnant women (who account for 25% of all cases of listeriosis) may harbor the organism asymptomatically in their genital tract and rectum and transmit the infection to their infants. Adults younger than 50 years with *Listeria* meningitis should be screened for HIV infection.[120] Meningitis can also occur in immunocompetent children and adults.[121,122] Outbreaks of *Listeria* infection have been associated with the consumption of contaminated coleslaw, raw vegetables, milk, and cheese, with sporadic cases traced to contaminated turkey franks, alfalfa tablets, cantaloupe, diced celery, hog head cheese (a meat jelly made from hog heads and feet), and processed meats, thus pointing to the intestinal tract as the usual portal of entry.[117–119,123–126]

Streptococcus agalactiae (Group B *Streptococcus*)

Group B streptococci are a common cause of meningitis in neonates,[127] with 52% of all cases in the United States reported during the first month of life.[51] In a review of 444 cases of neonatal bacterial meningitis over a 7-year period, group B streptococci were the most common cause in early-onset (occurring between birth and day 4 of life) and late-onset (occurring between days 5 and 28 of life) disease, responsible for 77% and 50% of cases, respectively.[128] In the United States, the overall mortality rate ranges from 7% to 27%.[48–51] Survivors of group B streptococcal meningitis also have substantial long-term morbidity,[129] indicating the need for ongoing developmental follow-up and the development

of preventive strategies (see later discussion). Group B streptococci have been isolated from vaginal or rectal cultures of 15% to 35% of asymptomatic pregnant women[130]; colonization rates do not vary during pregnancy, and carriage may be chronic (40%), transient, or intermittent. The risk for transmission from mother to infant is increased when the inoculum of organisms and the number of sites of maternal colonization are increased; the route of delivery does not influence transmission. Intrapartum antibiotic prophylaxis was introduced in several high-income countries in the 1990s.[131] A study of 848 cases in newborns and infants in France documented that antibiotic prophylaxis was associated with a decrease in early-onset cases (0–6 days old) but with a concomitant increase in late-onset cases (7–89 days).[131] Most of the cases were caused by subtype III organisms (83.9%). Group B streptococci can also cause meningitis in adults.[132–135] Risk factors in adults include age older than 60 years, diabetes mellitus, pregnancy or the postpartum state, cardiac disease, collagen vascular diseases, malignancy, alcoholism, hepatic failure, renal failure, previous stroke, neurogenic bladder, decubitus ulcers, and corticosteroid therapy; in one review of group B streptococcal meningitis in adults, no underlying illnesses were found in 43% of patients.[133]

Aerobic Gram-Negative Bacilli

Aerobic gram-negative bacilli (e.g., *Klebsiella* spp., *E. coli, Serratia marcescens, Pseudomonas aeruginosa, Acinetobacter* spp., *Salmonella* spp.) have become increasingly important as etiologic agents in patients with bacterial meningitis.[136–139] These agents may be isolated from the CSF of patients after head trauma or neurosurgical procedures[140–143] and may also be found in neonates, older adults, immunosuppressed patients, and patients with gram-negative sepsis. Some cases have been associated with disseminated strongyloidiasis in hyperinfection syndrome, a condition in which meningitis caused by enteric bacteria occurs secondary to seeding of the meninges during persistent or recurrent bacteremias associated with the migration of infective larvae.[144] Alternatively, the larvae may carry enteric organisms on their surfaces or within their own gastrointestinal tracts as they exit the intestine and subsequently invade the meninges. In patients with *E. coli* meningitis, 75% of cases are caused by strains possessing the K1 antigen.[127] Almost half of pregnant women have this organism isolated on rectal culture, and as many as 75% of their infants will be colonized during the first days of life; horizontal transmission from nursery staff members or other infants has also been reported.

Staphylococci

Meningitis caused by *Staphylococcus aureus* is usually found in early postneurosurgical or posttrauma patients and in those with CSF shunts; other underlying conditions include endocarditis, diabetes mellitus, alcoholism, chronic renal failure requiring hemodialysis, injection drug use, and malignancies.[145–148] In both adults and children, *S. aureus* is seen more frequently in patients with health care–associated ventriculitis and meningitis.[146,147] A study of 899 cases of nosocomial meningitis from Turkey showed that *S. aureus* accounted for 19% of cases.[148] Other sources of community-acquired *S. aureus* meningitis include patients with sinusitis, osteomyelitis, and pneumonia. Hospital-acquired cases are often caused by methicillin-resistant strains,[146] but recent a study documented that methicillin-susceptible strains caused two-thirds of pediatric cases.[147] In a multicenter review of 86 cases of methicillin-resistant *S. aureus* (MRSA) meningitis in adults,[146] the infection was nosocomial in 93% of cases; in those patients with postoperative meningitis, the most common predisposing conditions were the presence of CSF devices, neurosurgery, CSF leaks, and head trauma. Mortality rates have ranged from 14% to 77% in various series. In contrast, a pediatric study of 70 cases of *S. aureus* meningitis (75% were seen in patients with health care–associated ventriculitis and meningitis) found a low mortality rate (1.4%).[147] *Staphylococcus epidermidis* is the most common cause of meningitis in patients with CSF shunts (see Chapter 92).

Other Bacteria

A review of 28 cases of nocardial meningitis revealed predisposing conditions in approximately 75% of patients,[149] including immunosuppressive drug therapy, malignancy, head trauma, CNS procedures, chronic granulomatous disease, and sarcoidosis. Anaerobic meningitis is unusual and is generally associated with contiguous foci of infection (e.g., otitis, sinusitis, pharyngitis, brain abscess, head and neck malignancy, recent head and neck surgery or wound infection, and CNS trauma and neurosurgery)[150–153]; in many cases, more than one organism may be recovered. A study has advocated routine testing for anaerobes in patients with meningitis.[154] Enterococci are unusual etiologic agents of bacterial meningitis; most adult patients have underlying illnesses with CNS devices.[155] Disease caused by vancomycin-resistant *Enterococcus faecium* (VRE) is associated with a high mortality rate (18%–25%).[155,156] Despite the frequency with which the viridans-group streptococci cause bacteremia, they are unusual causes of meningitis (0.3%–5% of culture-proven cases).[157] *Streptococcus salivarius* meningitis has been reported after spinal anesthesia[158,159] and myelogram procedures,[160] supporting the importance of appropriate infection control practices (i.e., masks, proper aseptic technique, and safe injection practice) in those who perform spinal procedures. Group A streptococcal meningitis is also unusual, generally found in association with pharyngitis, otitis media, and sinusitis.[161] Group C streptococcal species (*Streptococcus equi* subsp. *zooepidemicus*) are rare causes of meningitis but may occur in humans after contact with domestic animals (especially horses) or their unpasteurized products.[162,163] *S. suis* is the most frequent cause of bacterial meningitis in southern Vietnam and is associated with significant morbidity involving hearing loss[164]; the pig is the natural reservoir of this microorganism and the main source of human infection. Risk factors for *S. suis* meningitis include eating "high-risk" dishes (e.g., undercooked pig blood or pig intestine) popular in parts of Asia, occupational exposure to pigs, and exposures to pigs or pork in the presence of skin injuries.[165] Diphtheroids, particularly *Propionibacterium* (now *Cutibacterium*) *acnes,* have become important etiologic agents of meningitis in patients with CNS shunt infections (see Chapter 92). With continued increases in numbers of immunocompromised patients and use of invasive diagnostic or therapeutic devices within the CNS, other (more unusual) bacterial pathogens may be reported as etiologic agents of acute meningitis.

Spirochetal Meningitis

Treponema pallidum

T. pallidum disseminates to the CNS during early infection.[166] The organism can be isolated by animal inoculation from the CSF of patients with primary syphilis, and CSF laboratory abnormalities are detected in 5% to 9% of patients with seronegative primary syphilis. The actual rate of invasion of the CNS during these early stages is likely to be considerably higher, however. Clinical neurosyphilis can be divided into four distinct syndromes[166–168]: syphilitic meningitis, meningovascular syphilis, parenchymatous neurosyphilis, and gummatous neurosyphilis. Some overlap may be seen in the clinical and laboratory findings of these syndromes. The incidence of syphilitic meningitis is greatest in the first 2 years after infection and is estimated to occur in only 0.3% to 2.4% of untreated syphilis cases. In contrast, meningovascular syphilis is found in 10% to 12% of individuals with CNS involvement[169] and occurs months to years after syphilis acquisition (peak incidence, approximately 7 years). Parenchymatous neurosyphilis has two variants: general paresis and tabes dorsalis. Both are relatively rare today and do not become apparent until 10 to 20 years after the acquisition of infection. Gummas are late manifestations of tertiary syphilis and may occur anywhere; gummatous neurosyphilis is rare. The overall incidence of neurosyphilis has increased, with many of the cases reported in patients with HIV infection.[167–169] In one report, 90% of patients with HIV with early syphilis undergoing lumbar puncture had evidence of CNS infection.[168]

Borrelia burgdorferi

The nervous system is eventually involved clinically in at least 10% to 15% of patients with Lyme disease, either while erythema migrans is still present or 1 to 6 months later.[170–172]

A 1992 study used PCR assay to detect spirochetal DNA in CSF samples from 8 of 12 patients with acute (<2 weeks) disseminated Lyme borreliosis,[172] which indicates that *B. burgdorferi* usually invades the CNS early in infection.

Protozoal and Helminthic Meningitis

Amebas

Despite the hundreds of species of free-living amoebas that are known, only a few have been reported to infect humans.[169–173] The most important are in the genera *Naegleria, Acanthamoeba,* and *Balamuthia. Naegleria fowleri,* the main protozoan causing primary amebic meningoencephalitis (PAM) in humans, has been recovered from lakes, puddles, pools, ponds, rivers, sewage sludge, tap water, air conditioner drains, and soil. Sporadic cases of PAM occur when persons, usually children and young adults, swim or play in water containing the amebas or when swimming pools or water supplies have become contaminated, often through failure of chlorination. In one review of 111 cases reported in the United States from 1962 to 2008, cases were reported in most southern states and occurred primarily in previously healthy young males exposed to warm recreational waters, especially lakes and ponds, in warm weather locations during summer months.[172] Activities that increase insertion of water into the nasal cavities (e.g., water skiing and wakeboarding) may increase the risk for developing PAM.[173] Asymptomatic carriage by humans can also occur. Several cases have been reported in HIV-infected patients, all with advanced HIV disease at the time of amebic infection.[174]

Angiostrongylus cantonensis

Infection of humans by larvae of the nematode *A. cantonensis* can lead to the development of an eosinophilic meningitis, and it is the most common cause of eosinophilic meningitis outside Europe and North America.[175–181] Humans become infected by eating infected intermediate hosts (i.e., mollusks, such as snails and slugs) or paratenic (i.e., freshwater prawns, crabs, frogs, and planaria) hosts or by eating food such as leafy green vegetables contaminated by these hosts. The larvae invade the brain either directly from the bloodstream or after migrating through other organs before reaching the spinal cord and brain. Once in the CNS, the larvae mature into adult worms that migrate through the brain. *A. cantonensis* is widespread, and human infection is fairly common and reported from many parts of the world (e.g., Thailand, India, Malaysia, Vietnam, Indonesia, Papua New Guinea, Taiwan, China and the Pacific Islands, including Hawaii). The parasites may spread to many countries by rats moving freely from port to port on ships; the rat infection rate in urban Bangkok has reached about 40%. A large outbreak of *A. cantonensis* meningitis was described in North America in travelers who had visited the Caribbean[181]; in this outbreak, the lettuce in a Caesar salad shared by the case patients was the most likely mode of transmission. After this outbreak, parasitologic surveys documented *A. cantonensis* in the Jamaican rat and land snail populations.[182] Tourists and visitors to endemic areas are at risk for becoming infected with *A. cantonensis.*

Other infectious causes of eosinophilic meningitis include *Gnathostoma* species, *Baylisascaris procyonis, Toxocara* species, and *Taenia solium.*[170] These are discussed in detail in other chapters of this book.

PATHOGENESIS AND PATHOPHYSIOLOGY

Viral Meningitis

Initiation of Infection

After the colonization of selected mucosal surfaces in the body by various viruses, the host possesses numerous barriers to prevent viral entry.[182] For example, the respiratory tract contains a thin film of mucus and a mucociliary escalator that moves viral particles away from the lower respiratory tract; even if this barrier is crossed, alveolar macrophages are actively phagocytic for viral particles. Gastric acidity inactivates most swallowed viruses, and gastrointestinal enzymes and bile also disrupt viral envelopes, capsid proteins, and lipoprotein membranes; however, some nonenveloped, acid-resistant viruses (e.g., EVs, adenoviruses, reoviruses, parvoviruses) are adapted for replication in the gastrointestinal tract. When the host has had previous contact with the viral agent, the mucosa of the gastrointestinal and respiratory tracts may be coated with secretory immunoglobulin A (IgA), which neutralizes the virus and prevents attachment and subsequent cell penetration. If certain viruses are able to escape initial host defense mechanisms, they may replicate and disseminate with the potential for CNS invasion.

Viremia and Central Nervous System Invasion

After hematogenous dissemination of the virus, CNS infection may occur. Most neurotropic viruses first multiply at extraneural sites (initially at the portal of entry), establish viremia, and then cross the blood-brain barrier (BBB) to invade the CNS.[182,183] For example, EVs initially multiply in the peritonsillar lymphatics, Peyer patches, lamina propria of the intestine, and vascular and endothelial cells, depending on the particular agent. M cells may mediate virus penetration from the gut lumen to lymphoid cells. From this initial site, the virus then disseminates to vascular tissue (e.g., liver, spleen, and muscle), where further multiplication augments the viremia. After viremia, viral particles are normally cleared by the reticuloendothelial system, with the speed of removal directly related to virus size (i.e., large viruses are cleared more promptly from the bloodstream). Viruses may also elude host clearance by associating with certain cells. Some viruses (e.g., measles, herpes, mumps) grow in human leukocytes, which protects them from phagocytosis by the reticuloendothelial system, neutralization by circulating antibody, and inactivation by nonspecific serum inhibitors.

CNS invasion by viruses may occur via several mechanisms. Most viruses invade directly across cerebral capillary endothelial cells, the major site of the BBB. Some viruses directly infect cerebral microvascular endothelial cells before infection of adjacent glia and neurons,[182,183] whereas others initially infect glia without evidence of endothelial cell infection. Still other viruses may be carried between cerebral endothelial cells in infected leukocytes after BBB disruption. Another site of virus entry is the choroid plexus epithelium. Studies of mumps virus in hamsters have shown a sequence of infection from the choroid plexus to the ependyma to parenchymal cells; viral nucleocapsids have been found in the choroid plexus and ependymal cells of humans with mumps meningitis. Viruses may reach the CNS by spread along olfactory nerves.[182,183] In an experimental hamster model, intranasal inoculation of HSV and togaviruses led to early infection of the olfactory bulb, which could be inhibited by cutting the olfactory tracts or chemically treating the olfactory mucosa. Peripheral nerve spread by viruses may also lead to CNS invasion.

Virus Spread Within the Central Nervous System

Regardless of the mechanism of CNS invasion, the production of disease requires viral attachment to and penetration of susceptible cells, spread within the nervous system, and induction of cellular changes. Viral entry into the subarachnoid space via the choroid plexus leads to dispersion of virus within CSF in contact with meningeal and ependymal cells[182]; sequential spread of virus may then occur in a contiguous fashion to glia and neurons. Other viruses spread through extracellular gaps between cells and CNS processes (e.g., dendrites, axons, or glia), or they transit along the extensive axonal and dendritic ramifications of neurons by way of the glia, or they are carried by mobile leukocytes in the inflammatory response. Experimental evidence supports each mode of transit, and all may be involved to various degrees in different viral infections.

Once viral infection of the CNS occurs, inflammatory cells usually accumulate, although the mechanisms leading to recruitment of inflammatory cells and their role in viral CNS infections are only partially understood.[182,183] It appears that the initial inflammatory response is immunologically specific and consists of a population of lymphocytes sensitized by the virus. However, an inflammatory response may fail to develop in other viral CNS infections, and this may depend on host age rather than the virus itself. Sensitized lymphocytes probably respond to a virus-specific protein that diffuses or is transported to the luminal surface of the endothelium, with subsequent passage through endothelial cells and release of inflammatory cytokines.

After development of a CSF inflammatory response, alterations in the BBB permit the traversal into CSF of serum proteins, including immunoglobulins. In addition, local CNS immunoglobulin synthesis occurs as B cells enter the CSF and differentiate into plasma cells. Intracerebral synthesis of immunoglobulins also is reflected by an increase in the CSF-to-serum ratios of specific immunoglobulins that persist for several weeks after infection.[182] The production of oligoclonal IgG

proteins within the CNS has been demonstrated in patients with meningitis caused by mumps virus, VZV, and HIV.[21,26,184,185] Furthermore, elevated CSF concentrations of oligoclonal IgG may persist for up to 1 year in patients with mumps meningitis,[21] which suggests the possibility of viral persistence and ongoing antigenic stimulation.

An intact host immune response appears to be important for clearance of virus from the CNS[182,183]; T-cell responses appear to be more important than B-cell responses. Failure of an immune response to develop may be a result of immunologic tolerance, host immune defects, or the ability of the virus to escape immune surveillance. Chronic infections with VZV, CMV, adenovirus, and measles virus have developed in patients with depressed cell-mediated immunity.

The CNS may also form anatomic viral reservoirs for persistent viral infection. Zika virus (ZIKV), for example, can persist in CSF of infected rhesus monkeys for weeks after virus has been cleared from peripheral blood, urine, and mucosal secretions. ZIKV-specific neutralizing antibodies were correlated with rapid clearance of virus in peripheral blood but remained undetectable in CSF for the duration of the study.[186]

Bacterial Meningitis

Numerous investigations over the past 40 to 50 years have elucidated many of the pathogenic and pathophysiologic mechanisms operable in bacterial meningitis.[187–194] Fig. 87.1 shows a simplistic hypothetical scheme of these mechanisms.

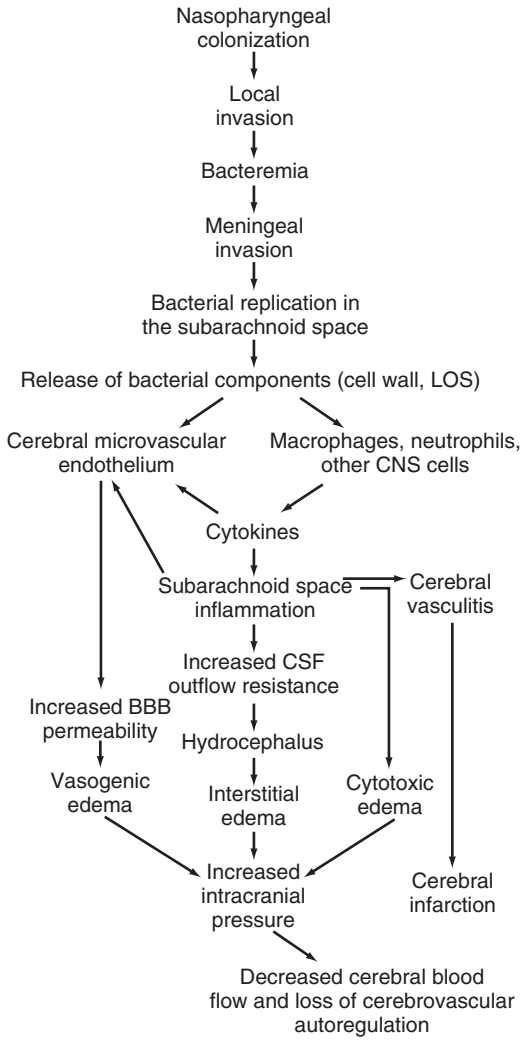

FIG. 87.1 Simplified scheme of the pathogenesis and pathophysiology of bacterial meningitis. *BBB,* Blood-brain barrier; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *LOS,* lipooligosaccharide. *(From Tunkel AR, Scheld WM. Pathogenesis and pathophysiology of bacterial meningitis.* Clin Microbiol Rev. *1993;6:118–136.)*

Mucosal Colonization and Systemic Invasion

The early pathogenic events that result in bacterial meningitis depend on an interplay between specific virulence factors and host defense mechanisms (Table 87.6). The initiation of infection with meningeal pathogens usually begins with host acquisition of a new organism by nasopharyngeal colonization.[189,195] Many of the major meningeal pathogens possess surface characteristics that enhance mucosal colonization. For example, the fimbriae (or pili) of *N. meningitidis* mediate adherence of this organism to nasopharyngeal epithelial cells; these fimbriated strains accounted for 80% of primary meningococcal isolates from nasopharyngeal carriers and from the CSF of patients with meningococcal meningitis. The fimbriae appear morphologically as aggregated bundles or single filaments. Once meningococci attach to nonciliated nasopharyngeal epithelial cells via a specific cell surface receptor (most likely CD46), they are transported across these cells within a phagocytic vacuole; this process appears to be essential for the subsequent development of invasive meningococcal disease. Studies have provided more information on the pathogenesis of meningococcal invasion. After attachment to the host endothelial cell, *N. meningitidis* induces formation of protrusions in the plasma membrane of host cells that aggregate bacteria into microcolonies and facilitate fimbriae-mediated contact between bacteria and between bacteria and host cells; after attachment and aggregation, organisms detach from the aggregates to systematically invade the host by means of a transcellular pathway that crosses the respiratory epithelium.[196] The detachment occurs with expression of pilin phosphotransferase, the enzyme that transfers phosphoglycerol onto pilin, altering the charge on the pilin structure and destabilizing pili bundles, thereby reducing bacterial aggregation and promoting detachment from the cell surface.[197]

Fimbriae have also been implicated in the attachment of *H. influenzae* to upper respiratory tract epithelial cells,[189] although fimbriae have not been found on isolates from the CSF or blood of patients with invasive disease. This observation suggests that although fimbriae play an initial role in adherence of *H. influenzae* within the nasopharynx, their presence is not necessary for the development of invasive disease, including meningitis. In addition, acquisition of and colonization by *H. influenzae* type b may be promoted after respiratory tract infection by viral agents such as the influenza A/Victoria virus and respiratory syncytial virus, although the precise role of a preceding upper respiratory viral infection in the enhancement of nasopharyngeal colonization by *H. influenzae*

TABLE 87.6 Selected Factors Involved in the Pathogenesis of Bacterial Meningitis

PATHOGENIC EVENT	BACTERIAL FACTORS	HOST FACTORS
Mucosal colonization	Fimbriae, polysaccharide capsule, IgA protease production, bacteriocins	Mucosal epithelium, secretory IgA, ciliary activity, anticapsular antibodies, pilin phosphotransferase
Intravascular survival	Polysaccharide capsule	Complement activation, organism-specific antibodies, TLR-9 single nucleotide polymorphisms, migration inhibitory factor single nucleotide polymorphisms
Meningeal invasion	Fimbriae, association with monocytes, *ibe10,* OmpA, extracellular loops of OmpA, platelet-activating factor receptor, pneumococcal choline-binding protein A, lipoteichoic acid, listeriolysin O, choline-binding protein CbpA, RrgA	Blood-brain barrier, cytotoxic necrotizing factor-1, cysteinyl leukotrienes, biopterin, cytosolic phospholipase $A_2\alpha$, β_2-adrenoceptor
Survival in the subarachnoid space	Polysaccharide capsule	Poor opsonic activity

type b is controversial. After nasopharyngeal colonization, invasion into the bloodstream by *H. influenzae* appears to occur via a breakdown in the tight junctions between epithelial cells, thereby leading to invasion by an intercellular mechanism.[195]

Surface encapsulation may also be an important virulence factor for nasopharyngeal colonization and systemic invasion of meningeal pathogens. In an experimental infant rat model, it was demonstrated that although all encapsulated strains of *H. influenzae* had the potential for systemic invasion after intraperitoneal inoculation, type b strains were the most virulent and were the only capsular types capable of systemic invasion after intranasal inoculation. Indeed, antibodies to type b capsule, which are almost uniformly detected in humans by the age of 4 years even in the absence of known exposure to *H. influenzae* type b, are protective against invasive disease. Polysaccharide capsule may also be an important virulence factor for the development of invasive disease by *S. pneumoniae.* In addition, in vivo capsular transformation events may equip pneumococcal strains with highly virulent blood-invasive phenotypes, thereby increasing the seriousness of pneumococcal infection, especially that caused by multidrug-resistant strains.[198]

Adherence of microorganisms to mucosal surfaces may be inhibited by natural antibodies found in mucosal secretions, such as IgA. However, it appears that the presence of high concentrations of circulating IgA antibodies to *N. meningitidis* may permit the development or progression of invasive disease by preferentially binding to the organism and blocking the beneficial effects of IgG and IgM antibodies.[187] In addition, species of many pathogenic bacteria (e.g., *Neisseria, Haemophilus, Streptococcus*) produce IgA1 proteases that cleave IgA in the hinge region and facilitate the adherence of bacterial strains to mucosal surfaces through local destruction of IgA. However, the exact role of IgA protease production in this pathogenic sequence remains unclear. The presence of anticapsular polysaccharide antibodies may also be effective in decreasing nasopharyngeal carriage of meningeal pathogens. In an intralitter transmission model in which infant rats were intranasally inoculated with *S. pneumoniae* and placed in a cage with other infant rats, pretreatment of uninoculated rats with systemic IgG antibodies to pneumococcal polysaccharide reduced the intralitter transmission of *S. pneumoniae*, which suggests that IgG antibodies to pneumococcal polysaccharide may be sufficient to reduce pneumococcal nasopharyngeal carriage in humans.

Intravascular Survival

Once bacteria cross the mucosal barrier and gain access to the bloodstream, they must overcome additional host defense mechanisms to survive. The presence of bacterial capsule, by effectively inhibiting neutrophil phagocytosis and resisting classical complement-mediated bactericidal activity, may enhance bloodstream survival of the organism, thereby facilitating intravascular replication.[188] The most common meningeal pathogens *(H. influenzae, N. meningitidis, S. pneumoniae, E. coli, S. agalactiae)* are all encapsulated. In addition, certain capsular types are disproportionately associated with the development of meningitis. For example, about 84% of cases of neonatal meningitis caused by *E. coli* are caused by strains bearing the K1 antigen; in the absence of specific host antibody to the K1 capsule, these organisms are profoundly resistant to phagocytosis. Presence of the K1 capsule and a high degree of bacteremia are key determinants in the development of *E. coli* meningitis.[199] It has been shown that *E. coli* strain C5, which causes neonatal meningitis, harbors a pathogenicity island designated PAI I_{C5} that contributes to the pathogenicity of *E. coli* meningitis by causing a high-grade bacteremia,[200] although further studies are needed to determine the importance of this factor in the development of *E. coli* meningitis.

The host possesses several defense mechanisms to counteract the antiphagocytic effects of the bacterial capsule.[189] For example, activation of the alternate complement pathway by the capsular polysaccharide of *S. pneumoniae* results in the cleavage of C3 with attachment of C3 to the bacterial surface.[189] This series of events facilitates opsonization, phagocytosis, and intravascular clearance of the organism. *H. influenzae* type b also activates the complement cascade. Experimental studies in a rat model have shown that after intravenous or intraperitoneal challenge with *H. influenzae* of varying serotypes (a, b, c, or d), a greater incidence and magnitude of bacteremia developed in rats depleted of C3. Although the incidence of bacteremia caused by type b organisms increased from 63% to 95% in complement-depleted rats, the incidence and severity of meningitis were unaffected by complement depletion. In an experimental study of pneumococcal meningitis in mice and rats, complement inhibition by C1 inhibitor was associated with reduced clinical illness, a less-pronounced inflammatory infiltrate around the meninges, and lower brain concentrations of proinflammatory cytokines and chemokines.[201]

Complement system activation is also an essential host defense mechanism against invasive disease caused by *N. meningitidis.* Patients with deficiencies in the membrane attack complex are particularly prone to neisserial infections, although usually with a more favorable outcome when appropriate therapy is instituted.[81] The reasons for the worse outcome in patients with an intact complement system are unclear, although a qualitative relationship can be shown among the concentration of circulating meningococcal lipooligosaccharide, a fatal outcome, and the degree of complement activation.[189]

The main cascade pathways activated after bacterial invasion of the bloodstream are the complement system, the inflammatory response, and the coagulation and fibrinolytic pathways, all of which are able to interact with one another. Genetic polymorphisms are among the components of these pathways (e.g., complement deficiencies and defects in sensing or opsonophagocytic pathways), and these are involved in determining the susceptibility to infection, along with the severity of disease and outcome.[202] Cytokines coordinate a wide variety of inflammatory reactions and have important roles in the initiation, maintenance, and termination of these reactions. Prominent proinflammatory cytokines include tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6. Essential parts of the inflammatory response include activation of coagulation and fibrin deposition, which shifts the hemostatic balance toward thrombosis.[203]

N. meningitidis can directly bind to factor H (fH), which is the main regulator of alternative complement activation, through surface molecules, including fH-binding protein (fHbp), neisserial surface protein A (NspA), and porin B.[102,103,203] The increase in the environmental temperature that occurs as the bacteria change habitat from the nasopharynx to the bloodstream has been identified as a "danger signal" for *N. meningitidis,* which prompts an upregulation of capsular biosynthesis and fHbp expression, thus enhancing its capacity to withstand complement attack.[203]

Meningeal Invasion

The mechanism by which meningeal pathogens gain access to the CNS has been the subject of intensive study; bacteria may potentially enter via intercellular (between cells) or transcellular (through cells) routes, leukocyte-facilitated mechanisms, or nonhematogenous routes by retrograde transport within cranial nerves.[204] The BBB is formed by microvascular endothelial cells and restricts invasion by bloodborne pathogens. Cerebral capillaries, as opposed to other systemic capillaries, have adjacent endothelial cells fused together by tight junctions that prevent intercellular transport, the virtual absence of pinocytotic vesicles, and a large quantity of mitochondria. Nevertheless, recent insight shows that pathogens can cross the BBB transcellularly, paracellularly, in infected phagocytes (i.e., via a "Trojan-horse" mechanism), or through a combination of these routes.[205] Some of these mechanisms are discussed in detail later.

The development of a sustained, high-grade bacteremia has been suggested as one important factor that leads to meningeal invasion.[189] In one study, culture-positive meningitis was produced in an experimental infant rat model only after an intense bacteremia had been present for at least 6 hours. In an experimental rat model of pneumococcal meningitis, attenuation of the bacteremic component of pneumococcal meningitis improved clinical symptoms and significantly reduced ventricular expansion and breakdown of the BBB,[206] suggesting that systemic infection contributes to the pathophysiology of bacterial meningitis. However, sustained bacteremia cannot be the sole factor responsible for meningeal invasion, because many other organisms (e.g., viridans-group streptococci) that produce high-grade bacteremia during infective endocarditis rarely produce meningitis. Studies have shown that a high degree of bacteremia is necessary, but not sufficient, for the

development of meningitis and that microbial binding to brain microvascular cells is needed, at least in vitro.[205]

The site of CNS invasion by meningeal pathogens is also unclear. Early studies suggested that invasion from the bloodstream was via the dural venous sinus system, whereas other experiments suggested that the site of invasion was above the cribriform plate or via the choroid plexus (because of their exceptionally high rate of blood flow of approximately 200 mL/g/min).[189] Experimental studies, however, have demonstrated that receptors for some meningeal pathogens are present on cells of the choroid plexus and cerebral capillaries. In cryostat sections of infant rat brain cortical slices, *E. coli* strains possessing S fimbriae have been shown to bind specifically to the luminal surfaces of the vascular endothelium and the epithelium lining the choroid plexus and brain ventricles. Phase variation to the nonfimbriated form may then be necessary for these bacteria to invade the CNS. To understand the cellular mechanisms important for meningeal invasion, the invasion of *E. coli* into endothelial and epithelial cell cultures was studied. It appeared that microtubule-dependent and/or microfilament-dependent pathways, which rearrange the cell cytoskeleton, may be important for bacterial uptake and crossing of the BBB.[207] *N. meningitidis* was also shown to adhere in vivo to the endothelium of both the choroid plexus and the meninges in a fatal case of meningococcemia[208]; isolates obtained from the CSF expressed significantly more PilC protein than did the blood isolates, which suggests that PilC plays an important role for this organism to cross the BBB. Despite these studies, the importance of adherence of meningeal pathogens to sites within the CNS requires further investigation.

Bacterial Survival Within the Subarachnoid Space

Once meningeal pathogens enter the subarachnoid space, host defense mechanisms are generally inadequate to control the infection.[205] CSF concentrations of complement components are absent or minimal; meningeal inflammation leads to increased, but low, CSF complement concentrations. This relative complement deficiency may be of critical importance because specific antibody or complement, or both, are essential for opsonization of encapsulated meningeal pathogens and efficient phagocytosis. Observations in experimental animal models and in patients with meningitis have revealed absent or barely detectable opsonic and bactericidal activity. The explanation for this low level of complement components during bacterial meningitis is unclear. It has been suggested that degradation of complement components crossing the BBB by leukocyte proteases may result in inefficient opsonic activity at the site of infection. Indeed, in an experimental rabbit model of pneumococcal meningitis, the intracisternal inoculation of a nonspecific protease inhibitor (phenylmethylsulfonyl fluoride) led to a decline in pneumococcal concentrations in CSF when compared with saline-inoculated controls.

Immunoglobulin concentrations are also low in normal CSF (blood-to-CSF ratio of IgG of about 800:1), and although concentrations increase during bacterial meningitis, they remain low in comparison with simultaneous serum concentrations.[189] In an experimental rabbit model, the intravenous administration of a bactericidal monoclonal antibody against the polyribosylribitol phosphate of *H. influenzae* type b produced high serum antibody concentrations, but BBB permeability was poor (5.5% or less) even in the presence of meningeal inflammation, which suggests that systemic administration of type-specific antibodies alone is likely to be suboptimal in therapy for bacterial meningitis.

Bacterial meningitis is characterized by the development of a neutrophilic pleocytosis within the CSF, although the precise mechanism of leukocyte traversal across the BBB is undefined.[189] The complement component C5a has been suggested to be one chemotactic component, with chemotactic activity appearing 2 to 4 hours before neutrophil influx into CSF. In an experimental rabbit model, the intracisternal inoculation of C5a led to an influx of leukocytes into CSF 1 hour after inoculation, a response that was attenuated by coadministration of prostaglandin E_2 (PGE_2) in a dose- and time-dependent manner, which suggests a direct antiinflammatory action of PGE_2 on C5a-induced CSF pleocytosis during bacterial meningitis. CSF C5 fragment concentrations in patients with bacterial meningitis have been correlated with several indicators of poor prognosis; a common nonsynonymous C5 SNP (rs17611) is associated with unfavorable outcome.[209] Consistent with these human data, C5a receptor–deficient mice with pneumococcal meningitis had lower CSF WBC counts and decreased brain damage compared with wild-type mice. Elevated CSF concentrations of two alternate pathway complement activation proteins, C3 and factor B, have also been found in mice and in patients with bacterial meningitis. In the mouse model of *Listeria* meningitis, intrathecal synthesis of C3 and factor B occurred during the course of the disease.

Despite this early influx of leukocytes in bacterial meningitis, host defense in CSF remains suboptimal because of the lack of functional opsonic and bactericidal activity. With inefficient phagocytosis, bacteria can multiply to huge concentrations in the CSF during meningitis.

Induction of Subarachnoid Space Inflammation

The induction of a marked subarachnoid space inflammatory response by meningeal pathogens contributes to many of the pathophysiologic consequences of bacterial meningitis and therefore to significant morbidity and mortality from this disorder. The invasion of leukocytes may contribute to the deleterious effects of inflammation within the brain with subsequent development of neuronal damage.[210] Experimental studies have focused on the virulence factors of meningeal pathogens and the specific inflammatory mediators that they induce (Table 87.7), in order to learn more about the mechanisms responsible for subarachnoid space inflammation. Replication and lysis of bacteria in the subarachnoid space lead to release of bacterial virulence components (e.g., peptidoglycan from gram-positive bacteria and lipooligosaccharide from gram-negative bacteria), which triggers the inflammatory response and production and release of inflammatory cytokines and chemokines.[211]

Alterations of the Blood-Brain Barrier

Bacterial meningitis has been shown to increase permeability across the BBB, which is composed of the arachnoid membrane, choroid plexus epithelium, and cerebral microvascular endothelium; the cerebral microvascular endothelium has been the site of intensive study in bacterial meningitis.[188,189] An adult experimental rat model was used to examine the propensity for meningeal pathogens to induce functional and morphologic alterations of the BBB. After intracisternal inoculation of *E. coli, S. pneumoniae,* or *H. influenzae* type b, alterations of the BBB were found with all three pathogens and manifested morphologically with an early and sustained increase in pinocytotic vesicle formation

TABLE 87.7 Potential Factors Contributing to Subarachnoid Space Inflammation

Bacterial Factors
Cell wall components
Lipooligosaccharide
Outer membrane vesicles
Peptidoglycan
Host Factors
Prostaglandins (PGE_2, prostacyclin)
Interleukins (IL-1β, IL-6, IL-8, IL-12, IL-16)
Interferon-γ
Growth-related gene product-α
Tumor necrosis factor-α
Platelet-activating factor
Transforming growth factor-1β
Macrophage inflammatory proteins 1 and 2
Leukocyte integrins (CD18)
Leukocyte selectins
Endothelial leukocyte adhesion molecule 1
Intercellular adhesion molecule 1 (ICAM-1)
Toll-like receptors (TLR2 and TLR4)
Complement components (C5a, C5b-9)
Substance P
Myeloid differentiation primary response protein 88 (MyD88)
Nuclear factor kappa B
Reactive nitrogen intermediates
Peroxynitrite

and progressive separation of intercellular tight junctions. These morphologic changes correlated with the functional penetration of albumin, a molecule normally excluded by an intact BBB, into the CSF. Intracisternal inoculation of an unencapsulated strain of *H. influenzae* caused an increase in pinocytotic vesicle formation without separation of intercellular tight junctions, which suggests that encapsulation of *H. influenzae* was not essential for BBB injury but facilitated its progression by avoidance of host defense mechanisms. The increased BBB permeability was observed in both normal and leukopenic animals, although permeability was augmented by the presence of leukocytes. The site of BBB injury was subsequently examined by in situ tracer perfusion and immunolabeling procedures to identify the topography and microvascular exit pathways of bovine serum albumin. Exit of both perfused colloidal gold bovine serum albumin and immunodetectable bovine serum albumin was through open intercellular junctions of venules in the pia-arachnoid, thus specifically and topographically localizing the BBB injury in bacterial meningitis to the meningeal venules.

Although most adjunctive strategies aim to attenuate the severity of CSF inflammation, findings in clinical and experimental studies of bacterial meningitis suggest that the inflammatory response might also have protective effects. A low CSF leukocyte count has been associated with an increased risk for adverse outcome in adults with pneumococcal meningitis. In addition, inhibition of different mediators implicated in the inflammatory response has led to aggravation of the disease and its complications in experimental pneumococcal meningitis. Although mice deficient in MyD88, a key adapter protein in Toll-like receptor (TLR)–mediated signaling pathways, showed diminished CSF inflammation, MyD88 deficiency was associated with poor outcome because of severe pneumococcal bacteremia.[212]

Cerebral Edema and Increased Intracranial Pressure

Cerebral edema is the major element contributing to increased intracranial pressure during bacterial meningitis and may result in life-threatening cerebral herniation and other complications.[189] The origin of the cerebral edema may be vasogenic, cytotoxic, or interstitial, or any combination of the three; all three elements probably contribute to cerebral edema during bacterial meningitis. Vasogenic cerebral edema is primarily a consequence of increased BBB permeability; cytotoxic cerebral edema results from swelling of the cellular elements of the brain, most likely through release of toxic factors from neutrophils, bacteria, or both; and interstitial cerebral edema reflects obstruction of the flow of normal CSF as in hydrocephalus. The last factor has been examined in an experimental rabbit model of pneumococcal or *E. coli* meningitis in which the CSF outflow resistance (defined as factors that inhibit the flow of CSF from the subarachnoid space to the major dural sinuses) was markedly elevated and remained elevated for as long as 2 weeks despite rapid CSF sterilization with penicillin therapy. In bacterial meningitis, cytotoxic edema appears to be facilitated by aquaporin-4, which facilitates water movement into brain astroglia and water movement out of the brain in vasogenic edema.[213]

These concepts have been examined in greater detail in an experimental animal model of pneumococcal meningitis in which brain water content (indicative of cerebral edema if elevated), CSF lactate concentrations, and CSF pressure were measured.[189] All three parameters were elevated in infected animals. Although treatment with ampicillin rapidly sterilized the CSF and normalized the brain water content and CSF pressure, the CSF lactate concentration remained elevated. The bacterial virulence factor responsible for the production of brain edema was subsequently examined in an experimental animal model of *E. coli* meningitis in which therapy with cefotaxime, but not chloramphenicol, induced a marked rise in CSF endotoxin concentrations that was associated with increased brain water content. The peptidoglycan of the *H. influenzae* cell wall also induced cerebral edema without perturbing the other parameters of inflammation (e.g., increased BBB permeability), which suggests that peptidoglycan induces cytotoxic rather than vasogenic cerebral edema. Neutrophils appeared to contribute to the development of cerebral edema if adequately stimulated, although the parameters of increased intracranial pressure and increased CSF concentrations of lactate and protein were unrelated to the presence of neutrophils. However, this area remains controversial because neutrophils are required for the increased BBB permeability seen in response to the intracisternal inoculation of bacterial virulence factors and inflammatory mediators.

Variability among bacterial strains may also be an important determinant in production of the subarachnoid space inflammatory response and brain edema in bacterial meningitis. Intracisternal inoculation of three different pneumococcal isolates resulted in pronounced differences in the pathophysiologic profiles 24 hours after challenge.[189] When pneumococcal cell wall fragments were inoculated intracisternally, the chemical composition of the fragments, specifically the degree of teichoication, influenced the induction of brain edema. In a subsequent study in an experimental rabbit model, serotype-specific characteristics of pneumococci were found to play a major role in the subarachnoid space inflammatory process, although significant differences in brain water content were observed only with one of the serotypes tested. It is unclear, however, whether these differences affect the clinical expression of disease in patients with bacterial meningitis.

The infusion of hypertonic mannitol to treat increased intracranial pressure has been evaluated in a rabbit model of *H. influenzae* type b meningitis.[189] In all animals, mannitol consistently reduced intracisternal pressure, although the magnitude of reduction was greater in infected animals, and brain water content was no different in mannitol-treated animals than in untreated ones. In contrast, in an experimental rat model of pneumococcal meningitis, mannitol modulated changes in cerebral blood flow, intracranial pressure, and brain water content, perhaps by a mechanism of scavenging hydroxyl radicals, which have been shown to be involved in the pathogenesis and pathophysiology of cerebral ischemia and neuronal injury in bacterial meningitis (see later discussion). In an experimental rabbit model of bacterial meningitis, use of adjunctive 3% hypertonic saline significantly elevated mean arterial pressure, reduced intracranial pressure, greatly improved cerebral perfusion pressure, inhibited brain aquaporin 4 expression, reduced cerebral edema, and attenuated brain damage with a superior effect over 20% mannitol.[214] Use of adjunctive glycerol in infant rats and adult mice with pneumococcal meningitis was not found to be beneficial.[215]

Alterations in Cerebral Blood Flow

Bacterial meningitis exerts profound effects on blood vessels that course through the subarachnoid space,[189] and the resulting vasculitis leads to narrowing or thrombosis of cerebral blood vessels and the propensity for ischemia and/or infarction of underlying brain. In combination with increased intracranial pressure, these changes may result in altered cerebral blood flow in patients with bacterial meningitis. An infant rhesus monkey model of *H. influenzae* meningitis demonstrated that cerebral cortical hypoperfusion occurs during meningitis and causes relative cerebral anoxia. Cerebrovascular autoregulation, in which cerebral blood flow is unchanged despite alterations of blood pressure over a wide range, is also lost during experimental bacterial meningitis. Furthermore, studies in an experimental rabbit model of pneumococcal meningitis demonstrated that animals given a lower intravenous fluid regimen (50 mL/kg/24 h) of normal saline had a lower mean arterial pressure, lower cerebral blood flow, and a higher concentration of CSF lactate than did animals that received a higher fluid regimen (150 mL/kg/24 h). In the first 4 to 6 hours of antibiotic administration, rabbits receiving lower fluid regimens had a significant decrease in mean arterial pressure and cerebral blood flow and a significant increase in CSF lactate concentrations when compared with rabbits receiving higher fluid regimens. These results, in combination with other experimental studies in which an increase in cerebral blood flow was noted within the first few hours of intracisternal inoculation of either live pneumococci or pneumococcal cell wall fragments, suggest that maintenance of adequate intravascular volume and minimization of stimuli that increase systemic blood pressure may be important in the treatment of bacterial meningitis. These findings may also be of potential clinical relevance inasmuch as inadvertent increases in mean arterial pressure directly increase cerebral blood flow and intracranial pressure, and depletion of intravascular volume with decreases in mean arterial pressure can cause parallel decreases in cerebral blood flow and a reduction in substrate delivery

to the brain. Therefore the brain is at risk from either hypoperfusion or hyperperfusion. As demonstrated by near infrared spectroscopy in conjunction with measurement of cerebral blood flow in an experimental rabbit model of pneumococcal meningitis, infected animals had a relative increase in the deoxygenated hemoglobin fraction and a decrease in the oxygenated hemoglobin fraction, thus supporting the possibility of cerebral venous engorgement in bacterial meningitis, which may contribute to intracranial hypertension in this disorder.

Cerebral blood flow has been measured in patients with bacterial meningitis. During the early phases of the disease, there is an increase in blood flow, whereas in advanced disease, cerebral blood flow is reduced.[216] In an early study,[189] measurement of cerebral blood flow (by the xenon 133 intraarterial injection method) revealed a 30% to 40% reduction in average total blood flow in five patients with pneumococcal meningitis (mean age, 54 years), but not in five patients with meningococcal meningitis (mean age, 20 years). An inverse relationship between cerebral blood flow and intracranial pressure has been observed in infants with bacterial meningitis; among eight patients, alterations were noted only in the four older infants (age range, 3–10 months) and not in the four neonates (age range, 5–30 days) in whom no changes in cerebral blood flow velocity were detected. In another study of 17 children (aged 8 days to 6 years) with bacterial meningitis, transcranial Doppler ultrasound monitoring demonstrated an improvement in cerebral blood flow velocity with resolution of meningitis. This observation suggests that in the early phase of bacterial meningitis, increased cerebrovascular resistance may contribute to a relative impairment in cerebral perfusion.

In a subsequent study in 20 children seriously ill with bacterial meningitis, total and regional cerebral blood flow measured with stable xenon computed tomography (CT) revealed a global decrease in flow and even more regional variability.[189] Although autoregulation of cerebral blood flow was preserved in the patients studied, hyperventilation reduced flow below the ischemic threshold, which raises important concerns about the routine use of hyperventilation in the management of increased intracranial pressure in patients with bacterial meningitis. In contrast, in another study of 9 patients with bacterial meningitis, 8 of whom had impaired cerebral blood flow autoregulation, autoregulation was partially or completely restored in 6 of 8 patients by short-term hyperventilation[217]; this recovery may protect the brain from fluctuations in perfusion pressure. In another study of 86 adult patients with bacterial meningitis, cerebral angiography was performed in 27 patients who had focal deficits (clinically, on cranial CT, or both) and who had persistent coma without an explained cause despite 3 days of antimicrobial therapy.[218] Thirteen of the patients who underwent angiography had alterations in their blood vessel system; the prognosis in these patients was poor. However, definitive changes in cerebral blood flow during bacterial meningitis are controversial and may vary with the stage of disease. These blood flow alterations may lead to regional hypoxia, increased lactate concentrations in the brain secondary to utilization of glucose by anaerobic glycolysis, and CSF acidosis, which may be a precursor to encephalopathy.[189]

CLINICAL MANIFESTATIONS

Viral Meningitis

Enteroviruses

The clinical manifestations of enteroviral meningitis depend on host age and immune status.[24,219,220] In neonates with proven enteroviral meningitis, fever is a ubiquitous finding and is usually accompanied by any combination of vomiting, anorexia, rash, and upper respiratory tract symptoms and signs. Neurologic involvement may be associated with nuchal rigidity and a bulging anterior fontanelle, although infants younger than 1 year are less likely to demonstrate meningeal signs. Mental status may be altered, but focal neurologic signs are uncommon.[220,221] A more severe form of meningoencephalitis may be seen in neonates, who appear to be at greatest risk for morbidity and mortality, particularly when symptoms and signs develop during the first day of life (after presumed transplacental transmission of the virus). With disease progression, a sepsis-like syndrome characterized by multiorgan involvement (e.g., hepatic necrosis, myocarditis, and necrotizing enterocolitis), disseminated intravascular coagulation, and cardiovascular collapse may develop. Findings in the CNS include seizures and focal neurologic signs. Lack of humoral antibody may contribute to the severity of neonatal infection.

The findings in neonates contrast to the clinical findings of enteroviral meningitis beyond the neonatal period (>2 weeks), in which severe disease and poor outcome are rare.[24,222] Infants usually present with fever, irritability, feeding difficulties, and rash; the majority of them have a good clinical outcome.[222] Approximately one-third of patients have stiff neck, and less than 2% of patients present with altered mental status.[30] A study of 187 children with meningitis identified the following variables to be associated with a positive CSF EV PCR assay result: May to November presentation, a CSF protein concentration <100 mg/dL, and normal findings on neurologic examination.[223] If ≤1 variable was present, the probability of having EV was 0%. This model could aid in deciding when to test patients with meningitis with an CSF EV PCR.

Headache is nearly always present in adults; photophobia is seen in approximately one-third of patients with EV meningitis.[30] Nonspecific symptoms and signs include vomiting, anorexia, rash, diarrhea, cough, upper respiratory tract findings (especially pharyngitis), and myalgias. Other clues to the presence of enteroviral disease include the time of year (more prevalent in the summer and autumn months), known epidemic disease in the community, exanthems, myopericarditis, conjunctivitis, and specifically recognizable enteroviral syndromes such as pleurodynia, herpangina, and hand-foot-and-mouth disease.[220] In addition, specific clinical stigmata may be associated with certain enteroviral serotypes.[220] For example, echovirus 9 is associated with scattered maculopapular rashes. Herpangina, in particular the finding of painful vesicles on the posterior oropharynx, is associated with coxsackievirus A; the presence of pericarditis or pleurisy may identify coxsackievirus B. The duration of illness in enteroviral meningitis is usually less than 1 week, with many patients reporting improvement after lumbar puncture, presumably from reduction in intracranial pressure. In contrast, during an outbreak of EV 71 infection in Taiwan in patients 3 months to 8.2 years of age, the chief neurologic complaint was rhombencephalitis (seen in 90% of children), which carried a case-fatality rate of 14%.[224] In another outbreak in young children with EV 71 infection in Perth, Western Australia,[225] neurologic syndromes included aseptic meningitis, Guillain-Barré syndrome, acute transverse myelitis, acute cerebellar ataxia, opsomyoclonus syndrome, benign intracranial hypertension, and febrile convulsions; this contrasts to previous epidemics, in which encephalitis was the most frequent syndrome of neurologic disease. In one prospective clinical study, brainstem encephalitis (which included signs such as myoclonic jerks, tremor or ataxia, cranial nerve palsies evident from eye movement disorders, facial weakness, and bulbar palsy) was the most frequent (58% of neurologic manifestations), followed by aseptic meningitis (36% of neurologic manifestations).[226]

A unique clinical situation is seen in children and adults with absent or deficient humoral immunity that impairs clearance of EVs. In persons who are agammaglobulinemic, a chronic enteroviral meningitis or meningoencephalitis may develop and last several years, often with a fatal outcome[219,220]; this syndrome has been designated chronic enteroviral meningoencephalitis in agammaglobulinemia (CEMA).[227] CEMA can manifest with headache, seizures, hearing loss, lethargy or coma, weakness, ataxia, paresthesias, loss of cognitive skills, and quadriplegia and can be fatal. Extraneurologic manifestations may include a chronic skin rash, fever, arthralgias, hepatitis, myositis, peripheral edema, endocrinopathies, retinopathy, and myocarditis.

Herpesviruses

Meningitis associated with HSV-2 infection is usually characterized by stiff neck, headache, and fever.[19,24] HSV-2 is the main cause of recurrent benign lymphocytic meningitis (Mollaret meningitis), which can develop in up to 10 recurrent episodes of meningitis that last 2 to 5 days followed by spontaneous recovery.[20] In sharp contrast to encephalitis, acyclovir has not been shown to improve outcomes in meningitis, a benign illness. The majority of patients are women in their fourth decade of life who have no active or history of genital herpes. HSV-1 and EBV can also occasionally cause recurrent meningitis.[20] VZV is the second most common herpesvirus causing aseptic meningitis, with the majority of cases occurring without the typical vesicular rash (zoster sine herpete).[228]

An acute presentation with a mononucleosis-like picture with rash, pharyngitis, lymphadenopathy, and splenomegaly should suggest EBV infection.[24]

West Nile virus

Neuroinvasive disease develops in approximately 1% of patients with WNV infections during the summer months in the United States.[27] Patients can present with meningitis, encephalitis, or AFP; up to 50% of patients with encephalitis have concomitant chorioretinitis.[229] Patients with meningitis typically present with fever, headache, nausea, vomiting, stiff neck, photophobia, and occasionally a maculopapular rash.[230] In addition, patients may have persistent headaches, abnormal neurologic examination findings, neurocognitive impairment, and chronic fatigue years after infection.[231,232]

Mumps Virus

In patients with mumps, CNS symptoms usually follow the onset of parotitis, when present, by about 5 days. The most frequent clinical manifestation of mumps CNS infection is the triad of fever, vomiting, and headache (Table 87.8).[233] The fever is usually high and lasts for 72 to 96 hours. Salivary gland enlargement is present in only about 50% of patients. Other findings include neck stiffness, lethargy or somnolence, and abdominal pain. Most patients have signs of meningitis but no evidence of cortical dysfunction. Defervescence is usually accompanied by clinical recovery, and in uncomplicated cases the total duration of illness is 7 to 10 days. Rarely, mumps may cause encephalitis, seizures, polyradiculitis, polyneuritis, cranial nerve palsies, myelitis, Guillain-Barré syndrome, and death.

Bacterial Meningitis

Patients with bacterial meningitis classically present with fever, headache, meningismus, and signs of cerebral dysfunction (i.e., confusion, delirium, or a declining level of consciousness ranging from lethargy to coma) (Table 87.9).[60] However, clinical presentation may vary based on age and underlying disease status and as a result of infection by specific bacterial pathogens.

TABLE 87.8 Presenting Symptoms and Signs in Patients With Central Nervous System Mumps

SYMPTOM OR SIGN	RELATIVE FREQUENCY (%)
Fever	88–100
Vomiting	68–94
Headache	47–88
Salivary gland swelling	47–62
Meningismus	43–93
Lethargy	28–69
Abdominal pain	14–23
Seizures	14–18

Modified from Gnann JW Jr. Meningitis and encephalitis caused by mumps virus. In: Scheld WM, Whitley RJ, Marra CM, eds. Infections of the Central Nervous System. *4th ed. Philadelphia: Lippincott Williams & Wilkins; 2014.*

TABLE 87.9 Presenting Symptoms and Signs in Patients With Bacterial Meningitis

SYMPTOM OR SIGN	RELATIVE FREQUENCY (%)
Headache	≥85
Fever	≥80
Meningismus	≥80
Altered sensorium	≥75
Vomiting	Approximately 35
Seizures	Approximately 30
Focal neurologic findings	10–35
Papilledema	<5

Neonates, Infants, and Children

The symptoms and signs of acute bacterial meningitis in neonates, infants, and children depend on the age of the child, duration of illness, and host response to infection[64,234]; the clinical manifestations can be subtle, variable, nonspecific, and even absent. For example, neonates with bacterial meningitis usually do not have meningismus.[235] Clinical clues to the presence of meningitis in neonates are temperature instability (hypothermia or hyperthermia), listlessness, high-pitched crying, fretfulness, lethargy, refusal to feed, weak suck, irritability, jaundice, vomiting, diarrhea, or respiratory distress. A change in the child's affect or state of alertness is one of the most important signs of meningitis. A bulging fontanelle (seen in one-third of cases in neonates) usually occurs late during the course of illness; seizures are observed in 40% of neonates with bacterial meningitis. In children 1 to 4 years of age, fever, vomiting, and nuchal rigidity are the most common initial symptoms.[234]

In a systematic review of 10 studies of prospective data on clinical manifestations suggestive of acute meningitis in children, bulging fontanelle, neck stiffness, seizures, and reduced food intake raised concerns for the presence of meningitis.[236] In children, the absence of meningeal signs and presence of an abnormal cry independently lowered the likelihood of meningitis, although the absence of fever did not exclude the diagnosis. In one review of children aged 2 months to 15 years who presented with suspected meningitis, the classic clinical signs had limited value in establishing the diagnosis.[237] Clinical examination revealed nuchal rigidity in 65% of those with meningitis; Brudzinski and Kernig signs (see later discussion) were elicited in 51% and 27% of those with meningitis, respectively. Accordingly, physicians should have a low threshold for performing lumbar puncture in patients at high risk for bacterial meningitis, given the serious nature of this disease.

Adults

In a review of 493 cases of acute bacterial meningitis in adults,[71] the triad of fever, nuchal rigidity, and change in mental status was found in only two-thirds of patients, but all had at least one of these findings. In a study of 1412 episodes of community-acquired bacterial meningitis in the Netherlands, the triad of fever, neck stiffness, and altered mental status was present in only 41% of episodes,[60] with the most common clinical manifestations being headache (83%), neck stiffness (74%), fever (74%), altered mental status (71%), and nausea (62%). The meningismus may be subtle, marked, or accompanied by the Kernig or Brudzinski sign or both.[238] The Kernig sign is elicited with the patient supine, with the thigh flexed on the abdomen and the knee flexed. The leg is then passively extended, and in the presence of meningeal inflammation, the patient resists leg extension. This technique differs somewhat from the maneuver as first described by Kernig, in which the patient was initially seated. Several signs were described by Brudzinski, although the best known is the nape-of-the-neck sign, in which passive flexion of the neck results in flexion of the hips and knees. However, in a prospective study of 297 adults with suspected meningitis, the diagnostic accuracy of meningeal signs was poor; both Kernig and Brudzinki signs had a 5% sensitivity, and nuchal rigidity a 30% sensitivity,[239] indicating that they did not accurately distinguish patients with meningitis from those without meningitis. Therefore the absence of these findings does not rule out the diagnosis of bacterial meningitis. Cranial nerve palsies (especially those involving cranial nerves III, IV, VI, and VII) and focal neurologic deficits (aphasia, hemiparesis, monoparesis) are seen in 9% and 22% of cases, respectively.[47] Cranial nerve palsies probably develop as the nerve becomes enveloped by exudate in the arachnoid sheath surrounding the nerve, or they may be a sign of increased intracranial pressure. Seizures occur in 14% of patients.[47] Focal neurologic deficits and seizures arise from cortical and subcortical ischemia, which results from inflammation and thrombosis of blood vessels, often within the subarachnoid space. In a study of 696 patients with community-acquired bacterial meningitis, cerebral infarction occurred in 174 (25%) episodes and was seen in 128 (36%) of 352 patients with pneumococcal meningitis[240]; an unfavorable outcome occurred in 62% of patients with cerebral

infarction. Diffuse cerebral disseminated intravascular coagulation may be another explanation for cerebral infarction complicating pneumococcal meningitis.[241] Papilledema is seen in less than 5% of cases early in infection, and its presence should suggest an alternative diagnosis. Hydrocephalus complicates 5% of episodes of community-acquired bacterial meningitis in adults and is associated with a high case-fatality rate.[242] With disease progression, signs of increased intracranial pressure may develop, including coma, hypertension, bradycardia, and palsy of cranial nerve III. Endocarditis complicates 2% of episodes of community-acquired bacterial meningitis in adults and is also associated with a high case-fatality rate[243]; clues suggesting the diagnosis of endocarditis in patients with bacterial meningitis are cardiac murmurs, persistent or recurrent fever, a history of heart valve disease, and *S. aureus* as the causative pathogen.

To further characterize the accuracy and precision of the clinical examination in adult patients with acute meningitis, 845 episodes of acute meningitis (confirmed with lumbar puncture or autopsy) in patients aged 16 to 95 years were reviewed[244]; the majority of patients in this review had acute bacterial meningitis, although 62 had tuberculous or "aseptic" meningitis. The results demonstrated that individual items of the clinical history (i.e., headache, nausea, and vomiting) had a low accuracy for the diagnosis of acute meningitis in adults. However, on review of the accuracy of physical examination findings, the absence of fever, neck stiffness, and altered mental status effectively eliminated the likelihood of acute meningitis; the sensitivity was 99% to 100% for the presence of one of these findings in the diagnosis of acute meningitis.

Older Adults

The clinical presentation in older adults differs significantly from that younger adults and represents a diagnostic challenge that can delay appropriate therapy.[245–247] In a study of 619 adults with community-acquired meningitis, elderly patients were less likely to complain of headache, stiff neck, photophobia, and nausea, but more likely to present with fever or with abnormal neurologic examination findings.[246] Elderly patients also had higher rates of abnormal cranial imaging findings and worse clinical outcomes. In another study of 696 adults with community-acquired bacterial meningitis, older adults were also less likely to complain of headache and stiff neck, but more likely to have sepsis and abnormal neurologic examination findings.[247] In a study of 185 patients 65 years of age and older, the diagnosis of community-acquired bacterial meningitis was more difficult because of the absence of characteristic meningeal signs[233]; compared with adult patients younger than 65 years, older patients showed greater neurologic severity, with a high number presenting with coma on admission, seizures, and hemiparesis. In a study of 160 adults with health care–associated ventriculitis or meningitis, older patients had more comorbidities, altered mental status, and worse CSF abnormalities (higher CSF pleocytosis and protein, and lower CSF glucose concentrations).[248]

Underlying Conditions

In patients with head trauma, the symptoms and signs of meningitis may be present as a result of the underlying injury and not meningitis.[70] In patients who have sustained a basilar skull fracture in which a dural fistula is produced between the subarachnoid space and the nasal cavity, paranasal sinuses, or middle ear, a common finding is rhinorrhea or otorrhea secondary to a CSF leak[70]; in these patients, meningitis may be recurrent and is most commonly caused by *S. pneumoniae.* Fortunately, the incidence of posttraumatic CSF leaks in patients with head trauma is low (0.1%–0.2%)[249]

The diagnosis of bacterial meningitis in neutropenic patients requires a high index of suspicion, because symptoms and signs may initially be subtle because of the impaired ability of the patient to mount a subarachnoid space inflammatory response.[189] In all of these subgroups of patients, altered or changed mental status should not be ascribed to other causes until bacterial meningitis has been excluded with CSF examination.

Pathogen-Specific Findings

A specific etiologic diagnosis in patients with bacterial meningitis may be suggested by certain symptoms or signs.[189] About 50% of patients with meningococcemia, with or without meningitis, present with a prominent rash located principally on the extremities. Early in the course of illness, the rash is typically erythematous and macular, but it quickly evolves into a petechial phase with further coalescence into a purpuric form. The rash often matures rapidly, with new petechial lesions appearing during the physical examination. In one review of the clinical manifestations of 255 patients with acute meningococcal meningitis,[250] a petechial rash was observed in three-fourths of the patients; the rash was more commonly seen in children and adults younger than 30 years (81%) than in patients 30 years and older (62%). However, others have observed a rash to be present in only up to 26% of cases and (if present) to be more likely to be scanty or more atypical than that seen in patients with meningococcal septicemia.[251] A similar rash may also be seen in splenectomized patients with rapidly overwhelming sepsis caused by *S. pneumoniae, H. influenzae* type b, or *Capnocytophaga canimorsus* (seen after a dog bite).

Patients with *L. monocytogenes* meningitis have an increased tendency to have seizures and focal deficits early in the course of infection, and some patients may present with ataxia, cranial nerve palsies, or nystagmus secondary to rhombencephalitis[117–119]; however, patients with *Listeria* meningitis may not present with any focal signs. In a large review of CNS infections caused by *L. monocytogenes,*[118] the most frequent findings were fever, headache, and altered sensorium but 42% had no meningeal signs. In a nationwide French study, a total of 818 cases of listeriosis were analyzed of which 252 (31%) were neurolisteriosis.[252] The majority of patients with neurolisteriosis presented with encephalitis (87%), with brainstem involvement in 17%. The most common findings were nuchal rigidity (65%), aphasia (19%), seizures (18%), and focal limb weakness (12%). Finally, another large study of 375 patients with neurolisteriosis in the Netherlands documented that mortality has remained high, especially in older patients and those with concomitant bacteremia.[54]

Spirochetal Meningitis

Treponema pallidum

The clinical manifestations of neurosyphilis that have been described are based on studies compiled before the availability of penicillin, and it is not known whether the clinical findings of symptomatic neurosyphilis have been modified in the antibiotic era or by associated HIV infection.[166] Although the clinical manifestations of neurosyphilis are numerous, only patients with acute meningitis and meningovascular syphilis are discussed here.

Patients with syphilitic meningitis usually present in a manner similar to that of patients with other forms of aseptic meningitis—that is, with complaints of headache, nausea, and vomiting. In one series, these complaints were present in 91% of patients.[237] Meningismus occurred in 59% and fever in less than half of the patients with syphilitic meningitis. Seizures occurred in 17% of patients, whereas cranial nerve palsies were found in 45% of cases (most commonly cranial nerves VII and VIII, followed by II, III, VI, and V). Focal abnormalities such as hemiplegia, aphasia, and mental status changes were seen less commonly. Syphilitic meningitis rarely affects the spinal cord.

Meningovascular syphilis is clinically distinguished from syphilitic meningitis temporally and on the basis of focal neurologic findings as a result of focal syphilitic arteritis, which almost always occurs in association with meningeal inflammation.[166] Most patients experience weeks to months of episodic prodromal symptoms and signs, including headache or vertiginous episodes, personality changes (e.g., apathy or inattention), behavioral changes (e.g., irritability or memory impairment), insomnia, or seizures. Focal deficits, which reflect episodes of ischemia in regions of the brain with involved blood vessels (usually in the distribution of the middle cerebral artery), may also occur; if untreated, these deficits may progress to a stroke syndrome with attendant irreversible neurologic deficits.

Coinfection with HIV may modify the clinical spectrum of syphilis. Case reports and small series have suggested that patients with HIV infection are more likely to progress to develop neurosyphilis and have accelerated disease courses.[167–169] However, few clinical data currently support these hypotheses. In one study of HIV-infected and HIV-uninfected patients with syphilis at sexually transmitted disease clinics

in Baltimore,[253] no significant differences were observed in clinical stage or in disease progression.

Neuroborreliosis

Neuroborreliosis due to *B. burgdorferi, Borrelia garinii,* or *Borrelia afzelii* is identified in approximately 15% of infected individuals.[254] Meningitis is the most common neurologic manifestation of acute disseminated Lyme disease, usually following erythema migrans by 2 to 10 weeks[170]; however, only about 40% (range, 10%–90%) of cases of Lyme meningitis are preceded by this characteristic rash.[170,171] Headache is the single most common symptom (30%–90% of patients) in Lyme meningitis, whereas neck stiffness is seen in only 10% to 20% of cases. Photophobia, nausea, and vomiting are intermediate in frequency between headache and neck stiffness. About two-thirds of patients have accompanying systemic symptoms, including malaise, fatigue, myalgias, fever, arthralgias, and involuntary weight loss. In untreated cases, the duration of symptoms ranges from 1 to 9 months. Patients typically experience recurrent attacks of meningeal symptoms lasting several weeks and alternating with similar periods of milder symptoms.[5,66,170,171,254]

About half of patients with Lyme meningitis have mild cerebral symptoms consisting most commonly of somnolence, emotional lability, depression, impaired memory and concentration, and behavioral symptoms.[170,254] These symptoms may fluctuate in severity in untreated patients before resolution. Transverse myelitis, spastic paraparesis or quadriparesis, disturbances of micturition, and Babinski sign are also reported during this stage. Approximately 50% of patients also have cranial neuropathies. Facial nerve palsy is the most common (80%–90%) of the cranial nerve palsies overall and occurs with rapid onset (often in 1–2 days), frequently accompanied by slight ipsilateral facial numbness or tingling or ipsilateral ear or jaw pain. The facial palsy is bilateral in 30% to 70% of cases, although the two sides are affected asynchronously in most cases. Other cranial nerves affected less commonly are cranial nerves II and III, the sensory portion of V, VI, and the acoustic portion of VIII. Recovery usually takes place within 2 months. In a large study of 431 patients with neuroborreliosis in Denmark, residual symptoms were seen in 28% and were associated with a delay in therapy.[254]

Protozoal and Helminthic Meningitis

Amebas

PAM occurs in two forms.[169–171] The acute form (incubation period, 3–8 days) is characterized by the sudden onset of high fever, photophobia, bifrontal or bitemporal headache, nuchal rigidity, and progression to stupor or coma and is usually indistinguishable from acute bacterial meningitis, although focal neurologic signs and seizures are more common in PAM. A review of 138 cases of PAM in the United States from 1962 to 2015 showed that the mortality rate was 97%; a few recent cases have been described in lakes in Minnesota (a result of global warming) and related to tap water.[255] Because of early involvement of the olfactory area, early symptoms of abnormal smell or taste may be reported. Confusion, irritability, and restlessness progress to delirium, stupor, and, finally, coma. Death in untreated patients generally occurs within 2 to 3 days from the onset of symptoms. The rapid progression of infection presents challenges to identify *N. fowleri* and initiate therapy before the onset of severe symptoms and death.[172] Therefore the key to early diagnosis is physician awareness and clinical suspicion.[256,257]

In contrast, the subacute or chronic form of PAM manifests more insidiously with low-grade fever, headache, and focal signs (e.g., hemiparesis, aphasia, cranial nerve palsies, visual field disturbances, diplopia, ataxia, seizures)[169,170]; the olfactory bulbs are usually spared. Deterioration occurs over a period of 2 to 4 weeks until death. However, longer durations of illness have also been reported (range, 5–18 months).

Angiostrongylus cantonensis

Symptoms of meningitis begin 6 to 30 days (typically 1–2 weeks) after the ingestion of raw mollusks or other sources of the parasite.[176–178] Findings include severe headache (90%), stiff neck (56%), paresthesias (54%), and vomiting (56%). Moderate fever is present in about half of the cases. In a recent outbreak in 12 people with a common foodborne exposure in Jamaica, the mean incubation period was 11 days (range, 6–31 days).[180] Headache was the most frequent symptom. Visual disturbances or photophobia were seen in 92% of patients, and nuchal rigidity or neck pain and fatigue were present in 80% of cases. Hyperesthesias or paresthesias were present in 75% of patients in a patchy distribution of the extremities or trunk and did not correspond to any dermatomal pattern. In a review of 18 cases in Hawaii from 2001 to 2005, 94% of patients had headache and 65% had sensory symptoms consisting of paresthesias, hyperesthesias, and/or numbness; those symptoms lasted a median of 17 and 55 days, respectively.[258] Disease usually resolves spontaneously after 1 to 2 weeks, but headaches and paresthesias can persist for weeks to months.[178]

DIAGNOSIS

The characteristics of diagnostic tests for categories of pathogens in patients with suspected meningitis are described here. It is important to note that many patients with community-acquired meningitis present with a negative Gram stain, largely because aseptic meningitis is so common.[2] The spectrum of causes in these patients is broad and, besides CSF culture for bacterial pathogens, molecular diagnostics using PCR has been developed to identify bacteria, viruses, and fungi. As individual PCRs for each pathogen in the differential diagnosis may be time consuming and expensive, several biotech companies have developed multiplex PCR panels with rapid turnover times. Developed multiplex assays include the BioFire FilmArray, Fast track, Seegene, and Taqman Array Card. The most studied and US Food and Drug Administration (FDA)-approved platform is the BioFire Meningitis/Encephalitis panel that detects six bacteria (*S. pneumoniae, N. meningitidis, S. agalactiae, H. influenzae, L. monocytogenes,* and *E. coli* K1), seven viruses (HSV-1 and HSV-2, HHV-6, CMV, EV, parechovirus, and VZV), and two fungi (*Cryptococcus gattii*/*Cryptococcus neoformans*); the test uses 0.2 mL of CSF and can provide results in 1 hour.[22,259–261] A strategy in which the panel was used in patients with meningitis with a negative Gram stain resulted in an increase of 22.9% in diagnoses rendered, mostly commonly viral pathogens, but also two cases with *S. pneumoniae* and a case of *C. gattii*/*C. neoformans*. However, 15.2% (5 of 33) of FA ME–negative isolates were positive according to standard assays (four cases of WNV and a case of *Histoplasma capsulatum*, pathogens not included in the panel).[259] In a retrospective analysis of CSF from HIV patients with cryptococcosis in Uganda, the test was considered useful in distinguishing culture-positive relapse from culture-negative immune reconstitution syndrome.[262] A multicenter prospective study of 1560 patients tested with the panel showed a high sensitivity and specificity for the 14 pathogens in the panel.[22] Of all of the assays, the most comprehensive one is the TaqMan Array Card, which includes 21 pathogens: 2 parasites (*Balamuthia mandrillaris* and *Acanthamoeba*), 6 bacteria (*S. pneumoniae, H. influenzae, N. meningitidis, Mycoplasma pneumoniae, Mycobacterium tuberculosis,* and *Bartonella*), and 13 viruses (parechovirus, dengue virus, Nipah virus, VZV, mumps virus, measles virus, lyssavirus, HSV-1 and HSV-2, EBV, EV, CMV, and chikungunya virus). These panels are probably very useful for ruling disease in, but are likely to be of limited value when negative. None of the panels so far have been studied in a randomized controlled trial to show effectiveness or in a prospective cost-effectiveness study.

Viral Meningitis

Cerebrospinal Fluid Examination

CSF pleocytosis is almost always present in patients with enteroviral meningitis, although some EVs have been isolated from young infants with clinical evidence of meningitis but no CSF WBCs.[220,260] A study of 390 patients with enteroviral meningitis showed that 16% to 18% of children and 68% to 77% of neonates had no CSF pleocytosis; younger age, lower serum WBC counts, and shorter duration of symptoms prior to the lumbar puncture were predictors for lack of CSF pleocytosis.[260] The cell count is usually 100 to 1000/mm,[3] although counts in the several thousands have also been reported.[220] EV can manifest with a neutrophilic pleocytosis in 39% of patients.[261] If a repeat lumbar puncture is done more than 8 hours later, the CSF WBC differential may change to a lymphocytic pleocytosis,[265] but this practice is done currently in only 0.5% of patients with a viral CNS infections.[261] However, in a recent retrospective chart review of 158 cases of meningitis (138 aseptic and 20 bacterial), 51% of the 53 patients with aseptic meningitis and duration

of symptoms of more than 24 hours had a neutrophil predominance in CSF,[266] suggesting that a CSF neutrophil predominance is not useful as a sole criterion in distinguishing between aseptic and bacterial meningitis. In addition, in one study of 65 infants younger than 3 months of age with enteroviral meningitis, 60% had no CSF pleocytosis.[267] This was also observed in another study of 60 patients, 23 of whom had no CSF pleocytosis[268]; those who lacked CSF pleocytosis were younger, had experienced more drowsiness, had lower peripheral WBC counts, and had a higher serum CRP concentration. Elevated CSF protein and decreased CSF glucose concentrations, if present, are usually mild, although extreme degrees of both have been reported. A specific virologic diagnosis of enteroviral meningitis depends on isolation of the virus from the CSF in tissue culture,[269] although the sensitivity for enteroviral serotypes is only 65% to 75%, largely a result of the inability to grow many coxsackievirus A serotypes, which require suckling mouse inoculations.[220,269] The difficulty in isolation of EVs from CSF may also relate to the low titers of EV in CSF (as low as a median tissue culture infective dose of 10 to 10^3/mL of CSF) and that no single cell line is optimal for the detection of all members of the genus.[220] Furthermore, the time required for identifying an EV from CSF using cell cultures is too long to be of clinical usefulness in establishing the diagnosis; the mean time for CSF EVs to grow is 3.7 to 8.2 days. In one study of viral cultures on 22,394 CSF samples, virus was recovered from only 5.7% of samples, most of which (98.4%) were EVs,[270] indicating that CSF viral cultures are insensitive for the diagnosis of viral meningitis. Although isolation of a nonpolio EV from the throat or rectum of a patient with aseptic meningitis is suggestive of an etiologic diagnosis, the mean shedding periods from those sites after infection are 1 week and several weeks, respectively. In addition, viral shedding can occur in 7.5% of healthy controls during EV epidemics.[220] Therefore shedding from a past infection cannot be ruled out. Furthermore, a study found that non-CSF viral cultures were not helpful in predicting enteroviral CNS infection, inasmuch as EVs were isolated at the same frequency from non-CSF sites in infants in whom EVs were cultured from CSF as in hospitalized infants with an acute illness whose CSF was negative. Follow-up acute and convalescent serologic testing for the specific isolated strain may confirm the etiologic diagnosis.[220] MRI of patients with rhombencephalitis has demonstrated high-intensity lesions in the brainstem, most commonly located in the tegmentum.[220]

Rapid diagnosis of EV infection through immunoassay techniques has been hampered by the lack of a common antigen among the various serotypes and the low concentrations of virus in body fluids.[17,220] Nucleic acid amplification tests, such as the PCR assay, have mostly replaced viral culture for the diagnosis of enteroviral meningitis. All the primers are directed at highly conserved regions of the 5′-noncoding region of the viral genome and designed for reverse transcription combined with PCR. Enteroviral reverse-transcriptase polymerase chain reaction (RT-PCR) has been tested in clinical settings by numerous investigators and found to be more sensitive than culture for the detection of the EV; the sensitivity has ranged from 86% to 100% and specificity from 92% to 100% for the diagnosis of enteroviral meningitis.[271–273] The Xpert enteroviral assay for detection of enteroviral RNA had a sensitivity of 94.7%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 98.2% for the diagnosis of enteroviral meningitis.[274] In addition, the time to identification of the EV with RT-PCR is significantly reduced (hours to a day) compared with cell culture, which may lead to shortened patient hospitalization, less use of antimicrobial agents for treatment of presumptive bacterial meningitis, and reduction of the need for ancillary diagnostic tests.[275] In one study in children with enteroviral meningitis with use of rapid enteroviral molecular tests (results are available within 3–24 hours), the median duration of hospitalization and duration of antimicrobial therapy were reduced to 2 days and 1 day, respectively.[276] EV-specific PCR tests do not detect HPeV, so testing for HPeV-specific PCR is required to detect these agents as a cause of viral meningitis.[22] In one study, HPeV-3 was detected in the CSF with PCR.[277] HPeV testing as part of the BioFire FA ME panel has shown excellent sensitivity.[22]

Patients with mumps meningitis almost always have CSF pleocytosis (usually <500/mm^3), primarily of mononuclear cells (>80% lymphocytes in 80%–90% of patients); the pleocytosis may persist for weeks. CSF protein concentrations are reported in some series to be normal in more than half of patients with mumps meningitis.[233] The CSF glucose content is normal in most patients, but it may be depressed in up to 25% of cases. Complement fixation and hemagglutination inhibition on serum specimens are the most reliable serologic tests for the diagnosis of mumps. Testing of paired acute and convalescent sera should demonstrate a diagnostic fourfold rise in mumps antibody titer. Mumps virus can be isolated from saliva from virtually all patients with mumps parotitis and can also be recovered in urine for up to 2 weeks after the onset of illness. Mumps virus can be grown from CSF in tissue culture for at least 1 week after the onset of disease, but the sensitivity of this technique is highly variable (30%–50% if collected from CSF early during the course of mumps CNS infection).[233] Application of molecular diagnostic techniques such as PCR assay (e.g., TaqMan array) may make enable the diagnosis of mumps to be made more quickly and more reliably in the future.[264]

Patients with HSV-2 meningitis also present most commonly with a lymphocytic meningitis (<500/mm^3) and a normal glucose content but can present with a mild hypoglycorrhachia (30–45 mg/dL) or with a neutrophilic pleocytosis.[19,261,278] CSF protein concentrations have been reported to be higher than in patients with enteroviral meningitis.[30] PCR has become the standard method of diagnosis for all herpesviruses (HSV-1, HSV-2, HHV-6, CMV, EBV, VZV). HSV-2 has now been identified as the main cause of Mollaret meningitis (i.e., recurrent benign lymphocytic meningitis) in patients without symptoms or signs of genital infection.[19,20] VZV PCR assay has also confirmed several cases of herpes zoster meningitis even without the typical vesicular rash (zoster sine herpete).[19,228]

Bacterial Meningitis

Cerebrospinal Fluid Examination

The diagnosis of bacterial meningitis rests on CSF examination by lumbar puncture[279–282]; typical CSF findings in acute bacterial meningitis are shown in Table 87.10. In virtually all cases, the opening pressure is elevated, with values over 600 mm H_2O suggesting the presence of cerebral edema, intracranial suppurative foci, or communicating hydrocephalus. The WBC count is elevated in untreated bacterial meningitis, usually 1000 to 5000/mm^3 (range, <100 to >10,000/mm^3); more than 90% of patients present with a CSF WBC count greater than 100/mm.^{3} Neutrophils usually predominate, although approximately 10% of patients with acute bacterial meningitis present with a predominance of lymphocytes in CSF; such predominance is more common in neonatal gram-negative bacillary meningitis and meningitis caused by *L. monocytogenes* (about 30% of cases). A study of 175 children with culture-proven bacterial meningitis showed that 16.2% of patients had a very low CSF white cell count (0–20/mm^3) and it was a predictor for a poor prognosis.[283] In adults, the absence of a CSF pleocytosis in pneumococcal meningitis is extremely rare (0.2%) but can account for almost 10% of all cases of meningococcal meningitis.[284,285] Therefore a Gram stain and culture should be performed on all CSF specimens even if the WBC count is normal. A CSF glucose concentration decreased to less than 40 mg/dL is found in about 60% of patients, and a

TABLE 87.10 Typical Cerebrospinal Fluid Findings in Patients With Bacterial Meningitis

CSF PARAMETER	TYPICAL FINDING
Opening pressure	200–500 mm H_2O
White blood cell count	1000–5000/mm^3 (range, <100 to >10,000)
Percentage of neutrophils	≥80%
Protein	100–500 mg/dL
Glucose	≤40 mg/dL
CSF-to-serum glucose ratio	≤0.4
Gram stain	Positive in 60%–90%
Culture	Positive in 70%–85%

CSF, Cerebrospinal fluid.

CSF-to-serum glucose ratio less than 0.25 occurs in 967 of 1412 (68%) patients.[60] CSF protein concentrations are elevated in virtually all patients, presumably because of disruption of the BBB. However, a normal CSF WBC count and protein concentration may be rarely seen in specimens obtained at the onset of meningitis, in some cases of neonatal meningitis, and in severely immunocompromised patients.

Gram stain examination of CSF permits rapid, accurate identification of the causative microorganism with sensitivity ranging from 20% in health care–associated ventriculitis and meningitis to 60% to 90% in patients with community-acquired bacterial meningitis, with a specificity of nearly 100%.[60,73] The likelihood of detecting the organism by Gram stain correlates with the concentration of bacteria in CSF; concentrations of 10^3 or fewer colony-forming units/mL are associated with positive Gram stains about 25% of the time, whereas CSF concentrations of bacteria of 10^5 or greater lead to positive microscopy results in up to 97% of cases.[267] The clinical usefulness of the Gram stain also depends on the bacterial pathogen.[260] Bacteria have been observed in 90% of cases of meningitis caused by *S. pneumoniae,* 86% of cases caused by *H. influenzae,* 75% of cases caused by *N. meningitidis,* and 50% of cases caused by gram-negative bacilli; the CSF Gram stain is positive in 24% to 32% of patients with *L. monocytogenes* meningitis.[236,252] CSF culture is the gold standard in diagnosis and is positive in 80% to 90% of patients with community-acquired bacterial meningitis if CSF is obtained before the start of antimicrobial therapy.[286] In a nationwide French study of 252 patients with neurolisteriosis, the diagnosis was established through CSF culture in 84%; in the other 16%, diagnosis was documented either with CSF PCR or with positive blood culture.[252] In health care–associated ventriculitis and meningitis, only 50% of patients have a positive CSF culture, most likely because of the frequent use of empirical antibiotic therapy before CSF studies are performed.[73] The probability of identifying the organism decreases significantly in patients who have received prior antimicrobial therapy (40%–60% and <50% positivity on Gram stain and culture, respectively), which resulted in the recommendation in the UK guidelines that a PCR assay be routinely performed for the two most common meningeal pathogens (*S. pneumoniae* and *N. meningitidis*) in patients presenting with meningitis.[287] In studies of infants and children with bacterial meningitis, initially positive CSF cultures became sterile in 90% to 100% of patients within 24 to 36 hours of administration of "appropriate" antimicrobial therapy.[288] Furthermore, it has been suggested that CSF sterilization may occur more rapidly after initiation of parenteral antimicrobial therapy than previously suggested, with complete sterilization of CSF containing meningococci within 2 hours, and the beginning of sterilization of pneumococci by 4 hours into therapy.[289] However, in most infants and children with bacterial meningitis who have received prior antimicrobial therapy, no significant differences in the CSF indices occur, although two studies revealed significantly lower CSF protein concentrations and rates of Gram stain positivity.[290]

Several rapid diagnostic tests have been developed to aid in the etiologic diagnosis of bacterial meningitis.[61,290] Latex agglutination techniques detect the antigens of *H. influenzae* type b, *S. pneumoniae, N. meningitidis, E. coli* K1, and the group B streptococci. However, many of the test kits do not include tests for group B meningococci, and other kits are probably poor because of the limited immunogenicity of group B meningococcal polysaccharide. The routine use of CSF bacterial antigen tests for the etiologic diagnosis of bacterial meningitis has been questioned.[290] In one study of 901 CSF bacterial antigen tests performed over a 37-month period, no modification of therapy occurred in 22 of 26 patients with positive results. False-positive results have occasionally resulted in unnecessary treatment and prolonged hospitalization.[291] Another study of 344 CSF specimens submitted for bacterial antigen assays found that 10 specimens represented true infections (by culture criteria), for a sensitivity and specificity of 70% and 99.4%, respectively[291]; a positive CSF antigen test did not affect clinical therapy or hospital course. Furthermore, in patients with culture-negative meningitis, CSF latex agglutination had a sensitivity of only 7% in one study.[292] Given that bacterial antigen testing does not appear to modify the decision to administer antimicrobial therapy and that false-positive results have been reported, routine use of this modality for rapid determination of the bacterial etiology of meningitis is not recommended, although it might be considered for patients who have been pretreated with antimicrobial therapy and when CSF Gram stain and culture results are negative.[293] An immunochromatographic test for detection of *S. pneumoniae* in CSF was found to be 100% sensitive and specific for diagnosing pyogenic pneumococcal meningitis,[294] although more studies are needed to demonstrate the usefulness of this test in the diagnosis of pneumococcal meningitis; the overall sensitivity of the test is 95% to 100%.[295] In another trial, this immunochromatographic test provided substantial benefit over latex agglutination tests and was positive in 99% of culture-positive cases of pneumococcal meningitis and negative in 99% of culture-confirmed cases caused by other pathogens.[296]

PCR assay has been used to amplify DNA from patients with meningitis caused by several meningeal pathogens and is now advocated in the United Kingdom guidelines.[287,297,298]

The clinical usefulness of PCR assay for the diagnosis of meningitis has been assessed with the use of a broad range of bacterial primers. The test characteristics for broad-based bacterial PCR demonstrated a sensitivity of 100%, a specificity of 98.2%, a positive predictive value of 98.2%, and a negative predictive value of 100%.[299] In another study with use of a multiplex PCR assay for detection of *N. meningitidis, S. pneumoniae,* and *H. influenzae* type b, the overall specificity and positive predictive value were 100% and the negative predictive value was 99.1% to 99.5%.[300] Multiplex assays for detecting genes of meningeal pathogens were 100% specific for detecting target organisms or serogroups, and the lower limit of detection was similar to that for the singleplex assays.[301] In another study, the sensitivity of broad-range PCR was higher than that of culture (59% vs. 43%), whereas the specificity was 97% for both methods of diagnosis.[302] Therefore broad-based bacterial PCR assay can be used to detect the most common microorganisms in only one test and has adequate sensitivity and excellent specificity[282]; these tests can be done within 2 hours in most industrialized countries, although they are scarce in resource-poor countries. PCR assay may be particularly useful in patients with bacterial meningitis who have received prior antimicrobial therapy and are more likely to have negative CSF cultures.[303] The test is rapid, is able to detect low numbers of bacteria, and detects nonviable etiologic agents in patients who have received prior antimicrobial therapy. The sensitivity and specificity of PCR assay in CSF for the diagnosis of pneumococcal meningitis are 92% to 100% and 100%, respectively.[295] Real-time PCR assay has also been used for the diagnosis of *L. monocytogenes* meningoencephalitis and is also included in the BioFire FA ME panel.[252,259,304] Problems with false-positive results arise with use of the PCR test, although further refinements in this technique may lead to its usefulness in the diagnosis of bacterial meningitis, particularly when CSF Gram stain and cultures are negative. Another potential application of the PCR assay is rapid detection of the in vitro susceptibility of meningeal pathogens to specific antimicrobial agents. In one report, a novel real-time PCR-hybridization assay was developed for the rapid detection of penicillin susceptibility in *S. pneumoniae*; when applied to 24 pneumococcal DNA-positive CSF extracts, penicillin-sensitive *S. pneumoniae* was detected in all instances.[305] Further studies may establish the usefulness of this rapid technique in allowing clinicians to decide on the use of specific antimicrobial therapy in patients with bacterial meningitis or to use or avoid adjunctive dexamethasone (see later discussion).[306]

Differentiation of Bacterial From Viral Meningitis

In patients without a positive CSF Gram stain or culture, the diagnosis of acute bacterial meningitis is often difficult to establish or reject. The most common etiologies for meningitis in the United States in both adults and children are viral; the majority of these patients receive empirical antibiotic therapy.[35,308] A combination of clinical manifestations, with or without test results, has been assessed to develop models in an attempt to accurately predict the likelihood of bacterial meningitis compared with other potential causes (most often viruses).[282] In one analysis of the records of 422 immunocompetent patients older than 1 month of age with acute bacterial or viral meningitis, it was found that CSF glucose concentration less than 34 mg/dL, a CSF–to–blood glucose ratio less than 0.23, a CSF protein concentration greater than 220 mg/dL, more than 2000 leukocytes/mm^3 of CSF, and more than 1180 neutrophils/mm^3

of CSF were individual predictors of bacterial rather than viral meningitis, with 99% certainty or better.[309] This model has been validated in several retrospective studies.[310] Many other prediction models have been developed and studied.[282] In a meta-analysis of bacterial meningitis score validation studies in which 5312 patients were identified from eight studies, 4896 (92%) had sufficient clinical data for calculation of the bacterial meningitis score, which identified children with CSF pleocytosis who were at very low risk for bacterial meningitis (low-risk features were negative CSF Gram stain, CSF absolute neutrophil count <1000 cell/mm,[3] CSF protein <80 mg/dL, and peripheral absolute neutrophil count <10,000 cells/mm^3).[311] Not surprisingly, one of the most important predictors for bacterial meningitis in this scoring system is a positive Gram stain, wherein the diagnosis is not a dilemma to clinicians. This scoring system has a combined sensitivity of 99.3%, with specificity of 62.1% and negative predictive value of 99.7%, indicating that this scoring system could be used to assist clinical decision making for the management of children with CSF pleocytosis. Despite the positive results of this meta-analysis and other studies, clinical judgment should continue to be used in decisions about the need for administration of empirical therapy in patients with suspected bacterial meningitis.[282] A study of 960 adults derived and validated a risk score in patients with meningitis and a negative Gram stain that identified a "zero risk" subgroup for any urgent treatable etiology (e.g., bacterial meningitis, herpes simplex encephalitis, fungal etiology) with 100% sensitivity.[312] Use of these models should be limited to the age cohort in which they were developed, but they could help clinicians in making a management decision.

Elevated CSF lactate concentrations may also be useful in differentiating bacterial from nonbacterial meningitis in patients who have not received prior antimicrobial therapy.[313–315] Two meta-analyses, one including 25 studies with 1692 patients (adults and children)[313] and the other including 31 studies with 1885 patients,[314] concluded that the diagnostic accuracy of CSF lactate is better than that of the CSF WBC count, glucose concentration, and protein level in the differentiation of bacterial from aseptic meningitis; sensitivities of 93% and 97% and specificities of 96% and 94%, respectively, were seen. In another study of adult patients with negative direct CSF examination, the most highly discernible parameter for the differential diagnosis of bacterial meningitis proved to be the CSF lactate value, with a sensitivity of 94%, specificity of 92%, negative predictive value of 99%, and positive predictive value of 82% at a cutoff of 3.8 mmol/L.[316] However, in patients who received antimicrobial therapy prior to lumbar puncture, CSF lactate concentrations had a substantially lower sensitivity of 49% compared with 98% in those not receiving antimicrobial pretreatment,[314] such that the usefulness of the CSF lactate value in patients pretreated with antimicrobial therapy is probably limited.

Several proteins have been examined for their usefulness in the diagnosis of acute bacterial meningitis. Specifically, CRP, detected either in serum or CSF, and serum procalcitonin concentrations have been elevated in patients with acute bacterial meningitis and may be useful in discriminating between bacterial and viral meningitis. In one study, serum CRP enabled Gram stain–negative bacterial meningitis to be distinguished from viral meningitis on admission with a sensitivity of 96%, a specificity of 93%, and a negative predictive value of 99%.[317] In another study, a serum procalcitonin concentration of more than 0.2 ng/mL had a sensitivity and specificity of up to 100% in the diagnosis of bacterial meningitis,[318] although false-negative results have been reported.[319] In another study, serum procalcitonin, at a cutoff of 0.28 ng/mL, had a sensitivity of 95%, specificity of 100%, negative predictive value of 100%, and positive predictive value of 97% in the diagnosis of bacterial meningitis.[316] In patients with meningitis in whom the CSF Gram stain is negative and analysis of other parameters is inconclusive, serum concentrations of CRP or procalcitonin that are normal or below the limit of detection have a high negative predictive value in the diagnosis of bacterial meningitis, so these patients (i.e., with a presumptive diagnosis of viral meningitis) can be carefully observed without initiation of antimicrobial therapy.[293,320] Finally, both CRP and procalcitonin have been used to assess the prognosis of patients with bacterial meningitis.[321,322]

Other markers that have been studied as markers for acute bacterial meningitis in children and adults include CSF concentrations of cortisol, heparin-binding protein, soluble triggering receptor expressed on myeloid cells 1 (TREM-1), IL-6, IL-12, IL-1β, TNF-α, complement factor B, and C3.[282] Most of these studies included low numbers of patients, limiting their generalizability. In one study, heparin-binding protein had a sensitivity of 100% and specificity of 99.2% in the differentiation of bacterial from aseptic meningitis.[323]

Radiography

Cranial CT or MRI does not aid in the diagnosis of acute bacterial meningitis and may be normal early in the course of infection. However, one of these modalities should be considered during the course of illness in patients who have persistent or prolonged fever, clinical evidence of increased intracranial pressure, focal neurologic findings or seizures, enlarging head circumference (in neonates), persistent neurologic dysfunction, or persistently abnormal CSF parameters or cultures (Fig. 87.2).[290] Gadolinium-enhanced MRI is the most sensitive modality for these complications, particularly with regard to infarction, especially when seen on diffusion-weighted imaging, and ventriculitis.[324] Magnetic resonance angiography and perfusion-weighted imaging may show vascular complications, including focal stenosis and irregularity of major intracranial arteries. However, cranial CT may underestimate the possibility of increased intracranial pressure in patients with pneumococcal meningitis,[325] so intracranial pressure monitoring should be considered in patients with prolonged coma. Cranial CT or MRI has been recommended at the end of antimicrobial therapy in neonates in order to be certain that no intracranial complications have occurred.[326] In one review of 107 children with bacterial meningitis who underwent CT,[327] one or more abnormalities were found in 52% of cases, although most findings did not require specific intervention. This lack of clinical utility was also seen in a study of 614 adults with community-acquired meningitis in which a head CT scan was done in 549 (89%) of patients; 15 patients (2.7%) had major intracranial findings that influenced clinical management in only 8 (1.5%) patients.[328]

Radiographic studies may be useful in the subset of patients with meningitis as a result of a basilar skull fracture with CSF leak.[114] CT may detect air-fluid levels, opacification of the paranasal sinuses, or intracranial air; CT with sagittal reconstruction can also be used to document or localize fracture sites. Radioisotope cisternography with cottonoid pledgets placed at the outlet of the sinuses within the nasal passage can be used to document a CSF leak, although high-resolution CT with water-soluble contrast enhancement of the CSF (metrizamide cisternography) is the best test for defining the site of leakage.

Spirochetal Meningitis

Treponema pallidum

For the diagnosis of CNS involvement in patients with syphilis, no single routine laboratory test is definitive. CSF cellular and protein abnormalities have been reported to occur in 10% to 20% of patients with primary syphilis, 30% to 70% of patients with secondary syphilis, and 10% to 30% of patients with latent syphilis.[166] CSF abnormalities are common in patients with syphilitic meningitis, but they are nonspecific. Findings include a mononuclear pleocytosis (>10 cells/mm^3 in most patients), elevated CSF protein concentrations (78% of patients), and mild decreases in CSF glucose concentrations (<50 mg/dL in 55% of patients).[237] A lack of CSF pleocytosis can also be seen in 22% of patients with documented neurosyphilis.[1] Oligoclonal bands and intrathecally produced antitreponemal antibodies are frequently present. Recovery of *T. pallidum* from CSF specimens through animal inoculation is difficult, expensive, time-consuming, and not routinely performed.[166]

The initial test for syphilis has become the enzyme-linked immunosorbent assay (ELISA) IgG, using recombinant proteins of *Treponema pallidum*. This test is considered sensitive but not specific. A positive serum ELISA is reflexed to a nontreponemal test, which is less sensitive but more specific, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test. If the result of this test is negative, a treponemal test is used for confirmation, such as the fluorescent treponemal antibody absorption (FTA-ABS) test, *T. pallidum* particle agglutination assay (TPPA), or chemiluminescense immunoassay (see Chapter 237).[166,237] However, serologic testing of CSF in patients with syphilis is problematic. For example, CSF collected by means of lumbar puncture is subject to blood contamination in about 10% of

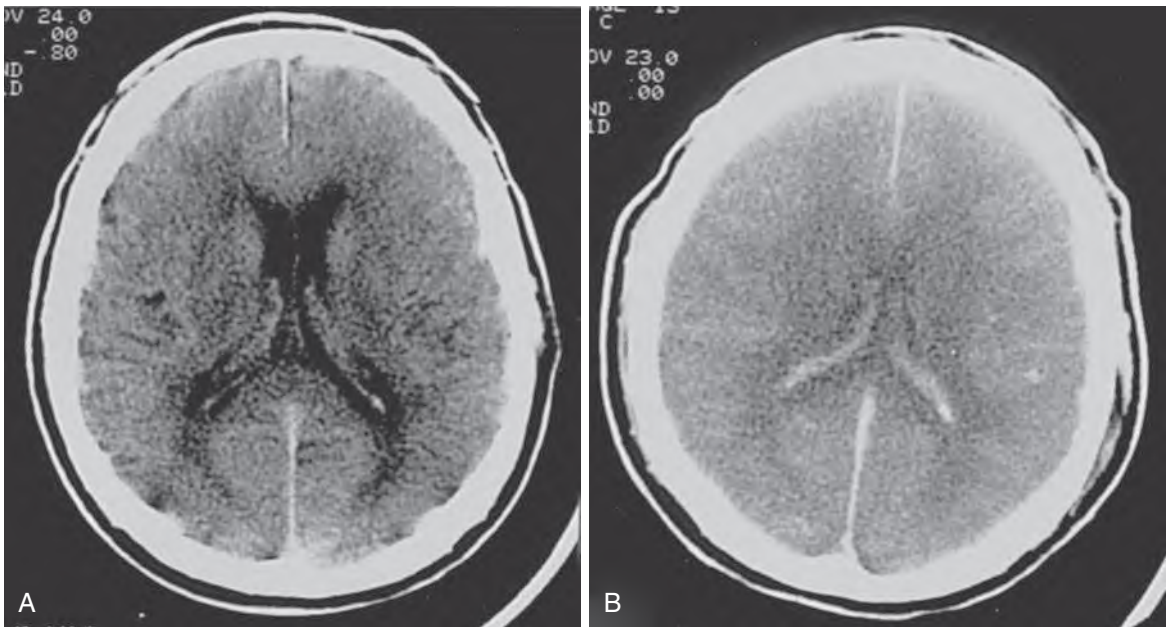

FIG. 87.2 Computed tomography (CT) scans of the head in a patient with pneumococcal meningitis. (A) CT scan on presentation reveals moderate cortical atrophy. (B) CT scan 3 days later reveals diffuse swelling of the cerebral hemispheres bilaterally, with effacement of the ventricular system.

patients, which may lead to contamination of CSF and therefore a false-positive serologic test result[166,329]; the likelihood of a false-positive test result depends on the relative amount of contamination, the antibody titer in blood, and the sensitivity of the test. For patients with a serum VDRL value of 1:256 or less, sufficient blood contamination to be visible to the naked eye is required for the result of the CSF VDRL test to be falsely positive. Although the specificity of the CSF VDRL test for the diagnosis of neurosyphilis is high, the sensitivity is low (reactive tests in only 30%–70% of patients).[166] Therefore a reactive CSF VDRL test in the absence of blood contamination is sufficient to diagnose neurosyphilis; a nonreactive result does not exclude the diagnosis. The CSF FTA-ABS test has also been examined as a possible diagnostic test for neurosyphilis.[166,329] A nonreactive test effectively rules out the likelihood of neurosyphilis, but the specificity of the test is much less than that of the CSF VDRL test because of the possibility of leakage of small amounts of antibody from the serum into CSF. Furthermore, no compelling data confirm the significance of a reactive CSF FTA-ABS as being useful for the diagnosis of neurosyphilis.[166] Other serologic tests that are currently being evaluated are the CSF-TPPA and the CSF *T. pallidum* hemagglutination assay (CSF-TPHA).[330] PCR has also been used to detect *T. pallidum* DNA in CSF samples in patients with neurosyphilis, with sensitivities of 69.7% to 75.8% and specificities of 86.8% to 92.3%.[331] Because of the low sensitivity of the CSF VDRL test, and until further studies demonstrate the usefulness of rapid diagnostic techniques, the diagnosis of neurosyphilis is based on elevated CSF concentrations of WBCs, protein, or both in the appropriate clinical and serologic setting.[166]

Borrelia burgdorferi

Typical CSF changes in patients with Lyme meningitis are a pleocytosis (usually <500 cells/mm^3 but up to 3500 cells/mm^3), with more than 90% lymphocytes in 75% of cases[170]; plasma cells may also be present. CSF protein concentrations are usually elevated (up to 620 mg/dL), and the CSF glucose concentration is usually normal, although it can be low in patients with illness of long duration. Oligoclonal banding may be present, with the bands reactive to *B. burgdorferi* antigens. Because viral meningitis is an important differential diagnosis in endemic areas, a clinical prediction rule has been used to help clinicians differentiate these two conditions. The "Rule of 7s" classifies children at low risk for Lyme meningitis when each of the following three criteria are met: <7 days of headache, <70% CSF mononuclear cells, and absence of seventh or other cranial nerve palsy.[332]

The best currently available laboratory test for the diagnosis of Lyme disease is demonstration of specific serum IgG antibody to *B. burgdorferi* by ELISA, followed by at least five bands on a Western blot. This positive test result in a patient with a compatible neurologic abnormality is strong evidence for the diagnosis.[170,333] However, these tests are not standardized, and marked variability is seen among laboratories.[254] Most laboratories now use an ELISA with sonicated *B. burgdorferi* as the antigen, although a few still use the immunofluorescence technique. By the time that subacute disseminated (i.e., stage II) disease has developed in most patients, serum concentrations of IgG antibody to *B. burgdorferi* are elevated. False-positive reactions have been reported in patients with rheumatoid arthritis, Rocky Mountain spotted fever, infectious mononucleosis, tuberculous meningitis, leptospirosis, yaws, syphilis, and relapsing fever,[170] although high titers of cross-reacting IgG antibodies have been detected only in patients with syphilis or relapsing fever. False-negative results may be obtained from an unreliable assay, early infection, or early antibiotic use, which may blunt the normal humoral immune response. It is currently recommended that when the pretest probability of Lyme disease is 0.20 to 0.80, sequential testing with ELISA and Western blot is the most accurate method for ruling in or out the possibility of Lyme disease.[334,335] Interpretation of IgM Western blot to *B. burgdorferi* is more problematic because of false positives. The test should never be ordered without a positive IgM ELISA and only if symptoms have been present for less than 4 weeks. Persistence of IgM antibody for months or even years limits interpretation as a recent infection. The sensitivity of two-tier testing in one study of patients with later manifestations of Lyme disease was 100% and the specificity was 99%[336]; all patients had positive C6 peptide ELISA results. Omission of the first-tier ELISA or interpretation of the immunoblot with criteria that are not evidence based will potentially decrease the specificity of testing and are contributing factors to misdiagnosis[337]; a concern with IgM immunoblots in clinical practice has been many false-positive results caused by overreading of nonspecific weak bands. Only <1% of peripheral IgG filters into the CSF with an intact BBB, allowing for the ability to compare CSF and serum antibody concentrations and documenting intrathecal antibody (ITAb) production.[170] This method appears to identify virtually all patients with Lyme meningitis and in the European guidelines is required for definitive diagnosis of neuroborreliosis.[338] Intrathecal synthesis of antibodies can persist for several months to up to 10 years after successful diagnosis and therapy.[337] In addition, ITAb also has issues with false positives and