Diagnosis is typically made by culture of the organism or by a variety of investigational serologic tests.[235] Molecular diagnosis has also been reported.[243] Delays in presenting for care may also affect outcome. In the Thai report, patients with vascular disease presented to medical care on average 3 months after developing lower extremity claudication or ulceration.

Successful therapy currently relies on surgical control of the infection.[242,244] Good response in localized skin and soft tissue infection has been reported with the use of saturated solution of potassium iodide. Commonly available systemic antifungals have been ineffective both in vitro and in clinical use. In vitro studies have identified doxycycline, minocycline, tigecycline, linezolid, azithromycin, and clarithromycin as potentially useful agents.[245–247] In combination with other agents (in vitro), terbinafine and minocycline appear to be most promising.[245,248,249] An experimental vaccine has also been used, but the results are difficult to interpret.[235,239]

RHINOSPORIDIUM SEEBERI

Rhinosporidiosis is a chronic, usually painless localized infection of the mucous membranes. Formerly believed to be a fungus, the causative agent, *Rhinosporidium seeberi*, has also never been cultured. With 18S ribosomal DNA sequencing, this organism has been shown to be a protistan parasite in the class Mesomycetozoea.[250,251,252] Rhinosporidiosis occurs worldwide, and the greatest numbers of cases are found in southern India and Sri Lanka.[253–255] Disease affects the nose and nasopharynx most commonly, the ocular structures less commonly, and the skin more rarely. Disseminated disease is rare. Lasser and Smith[256] reviewed 28 US cases, finding 19 that affected the nose and 9 the conjunctiva, with 24 occurring in men and 4 in women. Lesions increase in size over months to years to form friable pedunculated masses, typically in the nose, upper airway, or conjunctiva.[257] Nasal lesions manifest as nasal obstruction or epistaxis.[258] One or more pedunculated or verrucous skin lesions, with or without nasal or conjunctival lesions, are occasionally observed.[259] In rare cases, polyps occur in the vagina, urethra, or penis. *Rhinosporidium seeberi* forms round, thick-walled cysts (sporangia) in the submucosa, varying in diameter from 100 to 350 µm, often visible through the mucosa as white dots. Mature cysts become filled with numerous spores (endospores), which on release become new cysts (Fig. 268.16). Treatment of choice is surgery with electrocoagulation of the lesion base.[257]

SUMMARY

Key features of the uncommon fungi in this chapter are listed in Table 268.2.

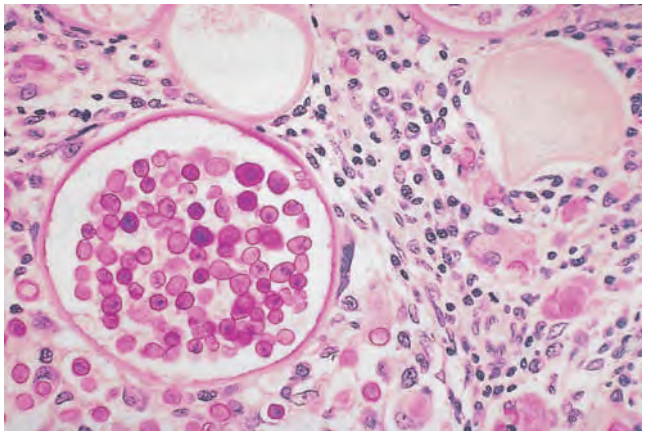

FIG. 268.16 Mature sporangium of *Rhinosporidium seeberi*. (Mayer mucicarmine stain.) *(From Watts JC, Chandler FW. Rhinosporidiosis. In: Connor DH, Chandler FW, Schwartz DA, et al, eds.* Pathology of Infectious Diseases. *Norwalk, CT: Appleton & Lange; 1997.)*

TABLE 268.2 Key Features of the Uncommon Fungi and Related Species

ORGANISM(S)	RISKS FACTORS/ RISK GROUPS	GEOGRAPHIC EPIDEMIOLOGIC RANGE	ECOLOGIC NICHE	CLINICAL MANIFESTATIONS	TISSUE FORMS	TREATMENT
Scedosporium apiospermum (P. boydii) species complex	Trauma, immunocompromise	Worldwide	Soil, fresh water, respiratory tract colonization	Pneumonia; osteoarticular, CNS, or disseminated infection; mycetoma	Septate hyphae	Voriconazole
Lomentospora (Scedosporium) prolificans	Severe immunocompromise, trauma	Worldwide	Soil, respiratory tract colonization	Disseminated infection, osteoarticular infection	Septate hyphae	Unknown (consider voriconazole and/ or high-dose L-AMB)
Dark-walled fungi (including *Alternaria, Bipolaris, Ochroconis, Cladophialophora, Curvularia, Exophiala, Exserohilum,* and *Wangiella* spp.)	Trauma, allergic rhinitis, immunocompromise	Worldwide	Soil, decaying organic matter, air, plants	Localized subcutaneous lesions, brain abscess, allergic sinusitis; disseminated infections (rare)	Septate hyphae; yeast or pseudohyphae (rarely)	High-dose D-AMB, L-AMB, itraconazole, or voriconazole
Fusarium spp.	Severe immunocompromise	Worldwide	Soil, plants	Disseminated infection, fungemia	Septate hyphae	High-dose D-AMB or L-AMB + voriconazole or posaconazole
Other opportunistic molds (including *Acremonium, Paecilomyces, Scopulariopsis,* and *Trichoderma*)	Severe immunocompromise	Worldwide	Soil, plants	Disseminated infection, fungemia	Septate hyphae	Based on species
Trichosporon spp.	Immunocompromise, central venous catheters	Worldwide	Skin and gastrointestinal flora	Fungemia	Yeast, hyphae, arthroconidia, pseudohyphae	Fluconazole or voriconazole or posaconazole
Malassezia furfur	Parenteral lipids	Worldwide	Skin	Catheter-related fungemia	Yeast	Catheter removal + voriconazole

Continued

TABLE 268.2 Key Features of the Uncommon Fungi and Related Species—cont'd

ORGANISM(S)	RISKS FACTORS/ RISK GROUPS	GEOGRAPHIC EPIDEMIOLOGIC RANGE	ECOLOGIC NICHE	CLINICAL MANIFESTATIONS	TISSUE FORMS	TREATMENT
Other opportunistic yeasts (including *Saprochaete/ Magnusiomyces* [*Blastoschizomyces*], *Pichia, Exophiala, Rhodotorula,* and *Saccharomyces*)	Immunocompromise, central venous catheters	Worldwide	Skin and/or environment	Catheter-related fungemia	Yeast	Catheter removal + antifungal based on species
Talaromyces (Penicillium) marneffei	AIDS	Southeastern Asia, southern China	Unknown	Disseminated infection	Yeasts or "sausage forms"	D-AMB ± 5-FC or itraconazole or voriconazole
Lacazia loboi	Rural outdoor labor, minor trauma	Central and South America	Unknown	Localized cutaneous/ subcutaneous infection	Chains of large yeasts	Surgery
Agents of adiaspiromycosis	Occupational inhalation	Worldwide	Dust	Pulmonary inflammation	Adiaspore (25–500 μm)	Corticosteroids
Emergomyces africanus	AIDS	South Africa	Soil	Disseminated infection	Yeasts	D-AMB followed by itraconazole
Prototheca spp.	Trauma	Worldwide	Water, soil, foodstuffs	Localized subcutaneous lesions	2–8 Endospores in sporangia	Surgery or itraconazole
Pythium spp.	Occupational trauma	Worldwide, Thailand	Likely aquatic	Vascular infection, ocular	Wide hyphae	Surgery
Rhinosporidium seeberi	Rural outdoor labor	India, Sri Lanka; rare worldwide	Unknown	Localized mucous membrane polypoidal lesions	Spores in large (100- to 350-μm) cysts (sporangia)	Surgery

AIDS, Acquired immunodeficiency syndrome; *CNS,* central nervous system; *D-AMB,* deoxycholate amphotericin B (1–1.5 mg/kg/day); *5-FC,* 5-fluorocytosine (should only be used when monitoring of levels is available locally); *L-AMB,* lipid preparations of amphotericin B (AmBisome, Abelcet).

Key References

The complete reference list is available online at Expert Consult.

1. Chen M, Zeng J, De Hoog GS, et al. The "species complex" issue in clinically relevant fungi: a case study in *Scedosporium apiospermum*. *Fungal Biol.* 2016;120:137–146.
3. Guarro J, Kantarcioglu AS, Horre R, et al. *Scedosporium apiospermum:* changing clinical spectrum of a therapy-refractory opportunist. *Med Mycol.* 2006;44:295–327.
5. Kantarcioglu AS, Guarro J, de Hoog GS. Central nervous system infections by members of the *Pseudallescheria boydii* species complex in healthy and immunocompromised hosts: epidemiology, clinical characteristics and outcome. *Mycoses.* 2008;51:275–290.
7. Miller MA, Greenberger PA, Amerian R, et al. Allergic bronchopulmonary mycosis caused by *Pseudallescheria boydii*. *Am Rev Respir Dis.* 1993;148:810–812.
8. Bates DD, Mims JW. Invasive fungal sinusitis caused by *Pseudallescheria boydii:* case report and literature review. *Ear Nose Throat J.* 2006;85:729–737.
10. Lamris GA, Chamilos G, Lewis RE, et al. *Scedosporium* infection in a tertiary care cancer center: a review of 25 cases from 1989-2006. *Clin Infect Dis.* 2006;43:1580–1584.
11. Castiglioni B, Dutton DA, Rinaldi MG, et al. *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*): infection in solid organ transplant recipients in a tertiary medical center and review of the literature. *Medicine (Baltimore).* 2002;81:333–348.
12. Bernstein EF, Schuster MG, Stieritz DD, et al. Disseminated cutaneous *Pseudallescheria boydii*. *Br J Dermatol.* 1995;132:456–460.
13. Larocco A, Barron JB. Endogenous *Scedosporium apiospermum* endophthalmitis. *Retina.* 2005;25:1090–1093.
14. Hung CC, Chang SC, Yang PC, et al. Invasive pulmonary pseudallescheriasis with direct invasion of the thoracic spine in an immunocompetent patient. *Eur J Clin Microbiol Infect Dis.* 1994;13:749–751.
15. Halpern AA, Nagel DA, Schurman DJ. *Allescheria boydii* osteomyelitis following multiple steroid injections and surgery. *Clin Orthop.* 1977;126:232–234.
16. Lavy D, Morin O, Venet G, et al. *Pseudallescheria boydii* knee arthritis in a young immunocompetent adult two years after a compound patellar fracture. *Joint Bone Spine.* 2001;68:517–520.
17. Tirado-Miranda R, Solera-Santos J, Brasero JC, et al. Septic arthritis due to *Scedosporium apiospermum:* case report and review. *J Infect.* 2001;43:210–212.
18. Montero A, Cohen JE, Fernandez MA, et al. Cerebral pseudallescheriasis due to *Pseudallescheria boydii* as the first manifestation of AIDS. *Clin Infect Dis.* 1998;26:1476–1477.
19. Bryan CS, DiSalvo AF, Kaufman L, et al. *Petriellidium boydii* infection of the sphenoid sinus. *Am J Clin Pathol.* 1980;74:846–851.
20. Dworzack DL, Clark RB, Borkowski WJ, et al. *Pseudallescheria boydii* brain abscess: association with near-drowning and efficacy of high-dose, prolonged miconazole therapy in patients with multiple abscesses. *Medicine (Baltimore).* 1989;68:218–224.
21. Benham RW, Georg LK. *Allescheria boydii,* causative agent in a case of meningitis. *J Invest Dermatol.* 1948;10:99–110.
22. Fernandez-Flores A, Lopez-Medrano R, Fuster-Foz C. Histopathological clues in the diagnosis of fungal infection by *Scedosporium* in a case of endophthalmitis starting as conjunctivitis. *J Cutan Pathol.* 2016;43:461–467.
23. Galgiani JN, Stevens DA, Graybill JR, et al. *Pseudallescheria boydii* infections treated with ketoconazole: clinical evaluations of seven patients and in vitro susceptibility results. *Chest.* 1984;82:219–224.
24. Piper JP, Golden J, Brown D, et al. Successful treatment of *Scedosporium apiospermum* suppurative arthritis with itraconazole. *Pediatr Infect Dis J.* 1990;9:674–675.
25. Barbaric D, Shaw PJ. *Scedosporium* infection in immunocompromised patients: successful use of liposomal amphotericin B and itraconazole. *Med Pediatr Oncol.* 2001;37:122–125.
29. Nesky MA, McDougal EC, Peacock JE Jr. *Pseudallescheria boydii* brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. *Clin Infect Dis.* 2000;31:673–677.
30. Poza G, Montoya J, Redondo C, et al. Meningitis caused by *Pseudallescheria boydii* treated with voriconazole. *Clin Infect Dis.* 2000;30:981–982.
32. Mellinghoff IK, Winston DJ, Mukwaya G, et al. Treatment of *Scedosporium apiospermum* brain abscesses with posaconazole. *Clin Infect Dis.* 2002;34:1648–1650.
33. Malloch D, Salkin IF. A new species of *Scedosporium* associated with osteomyelitis in humans. *Mycotaxon.* 1984;21:247–255.
34. Rodriguez-Tudela JL, Berenguer J, Guarro J, et al. Epidemiology and outcome of *Scedosporium prolificans* infection: a review of 162 cases. *Med Mycol.* 2009;47:359–370.
35. Wilson CM, O'Rourke EJ, McGinnis MR, et al. *Scedosporium inflatum:* clinical spectrum of a newly recognized pathogen. *J Infect Dis.* 1990;161:102–107.
36. Wood GM, McCormack JG, Muir DB, et al. Clinical features of human infection with *Scedosporium inflatum*. *Clin Infect Dis.* 1992;14:1027–1033.
37. Alvarez M, Ponga BL, Rayon C, et al. Nosocomial outbreak caused by *Scedosporium prolificans (inflatum):* four fatal cases in leukemia patients. *J Clin Microbiol.* 1995;33:3290–3295.
38. Bouza E, Munoz P, Vega L, et al. Clinical resolution of *Scedosporium prolificans* fungemia associated with reversal of neutropenia following administration of granulocyte colony-stimulating factor. *Clin Infect Dis.* 1996;23:192–193.
39. Kelly M, Stevens R, Konecny P. *Lomentospora prolificans* endocarditis – case report and literature review. *BMC Infect Dis.* 2016;16:36.
40. Farag SS, Firkin FC, Andrew JH, et al. Fatal disseminated *Scedosporium inflatum* infection in a neutropenic immunocompromised patient. *J Infect.* 1992;25:201–204.
41. Rabodonirina M, Paulus S, Thevenet F, et al. Disseminated *Scedosporium prolificans (S. inflatum)* infection after single-lung transplantation. *Clin Infect Dis.* 1994;19:138–142.
42. Madrigal V, Alonso J, Bureo E, et al. Fatal meningoencephalitis caused by *Scedosporium inflatum (Scedosporium prolificans)* in a child with lymphoblastic leukemia. *Eur J Clin Microbiol Infect Dis.* 1995;14:601–603.
43. Parize P, Boussaud V, Poinsignon V, et al. Clinical outcome of cystic fibrosis patients colonized by *Scedosporium* species following lung transplantation: a single-center 15-year experience. *Transpl Infect Dis.* 2017;19:e12738.
44. Schwarz C, Brandt C, Antweiler E, et al. Prospective multicenter German study on pulmonary colonization with *Scedosporium/Lomentospora* species in cystic fibrosis: epidemiology and new association factors. *PLoS ONE.* 2017;12:e0171485.
45. del Palacio A, Garau M, Amor E, et al. Case reports. Transient colonization with *Scedosporium prolificans:* report of four cases in Madrid. *Mycoses.* 2001;44:321–325.

46. Hopwood V, Evans EGV, Matthews J, et al. *Scedosporium prolificans,* a multi-resistant fungus, from a UK AIDS patient. *J Infect*. 1995;30:153–155.
47. Salkin IF, McGinnis MR, Dykstra MJ, et al. *Scedosporium inflatum,* an emerging pathogen. *J Clin Microbiol*. 1988;26:498–503.
48. Lennon PA, Cooper CR Jr, Salkin IF, et al. Ribosomal DNA internal transcribed spacer analysis supports synonomy of *Scedosporium inflatum* and *Lomentospora prolificans*. *Clin Microbiol*. 1994;32:2413–2416.
49. Ortoneda M, Capilla J, Pujol I, et al. Liposomal amphotericin B and granulocyte colony-stimulating factor therapy in a murine model of invasive infection by *Scedosporium prolificans*. *J Antimicrob Chemother*. 2002;49:525–529.
50. Capilla J, Yustes C, Mayayo E, et al. Efficacy of albaconazole (UR-9825) in treatment of disseminated *Scedosporium prolificans* infection in rabbits. *Antimicrob Agents Chemother*. 2003;47:1948–1951.
51. Afeltra J, Dannaoui E, Meis JF, et al. In vitro synergistic interaction between amphotericin B and pentamidine against *Scedosporium prolificans*. *Antimicrob Agents Chemother*. 2002;46:3323–3326.
52. Meletiadis J, Mouton JW, Meis JF, et al. In vitro drug interaction modeling of combinations of azoles with terbinafine against clinical *Scedosporium prolificans* isolates. *Antimicrob Agents Chemother*. 2003;47:106–117.
53. Meletiadis J, Mouton JW, Rodriguez-Tudela JL, et al. In vitro interaction of terbinafine with itraconazole against clinical isolates of *Scedosporium prolificans*. *Antimicrob Agents Chemother*. 2000;44:470–472.
54. Tong SYC, Peleg AY, Yoong J, et al. Breakthrough *Scedosporium prolificans* infection while receiving voriconazole prophylaxis in an allogeneic stem cell transplant recipient. *Transpl Infect Dis*. 2007;9:241–243.
55. Howden BP, Slavin MA, Schwarer AP, et al. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. *Eur J Clin Microbiol Infect Dis*. 2003;22:111–113.
57. Nucci M, Akiti T, Barreiros G, et al. Nosocomial fungemia due to *Exophiala jeanselmei* var. *jeanselmei* and a *Rhinocladiella* species: newly described causes of bloodstream infection. *J Clin Microbiol*. 2001;39: 514–518.
59. Jeon SJ, Nguyen TTT, Lee HB. Phylogenetic status of an unrecorded species of *Curvularia, C. spicifera,* based on current classification system of *Curvularia* and *Bipolaris* group using multi loci. *Microbiology*. 2015;43:210–217.
60. Rossman SNB, Cernoch PL, Davis JR. Dematiaceous fungi are an increasing cause of human disease. *Clin Infect Dis*. 1996;22:73–80.
62. Aldape KD, Fox HS, Roberts JP, et al. *Cladosporium trichoides* cerebral phaeohyphomycosis in a liver transplant recipient. *Am J Clin Pathol*. 1991;95:499–502.
63. Filizzola MJ, Martinez F, Rauf SJ. Phaeohyphomycosis of the central nervous system in immunocompetent hosts: report of a case and review of the literature. *Int J Infect Dis*. 2003;7:282–286.
64. Buxi TBS, Prakash K, Vohra R, et al. Imaging in phaeohyphomycosis of the brain. Case report. *Neuroradiology*. 1996;38:139–141.
65. Walz R, Bianchin M, Chaves ML, et al. Cerebral phaeohyphomycosis caused by *Cladophialophora bantiana* in a Brazilian drug abuser. *J Med Vet Mycol*. 1997;35:427–431.
66. Barron MA, Sutton DA, Veve R, et al. Invasive mycotic infections caused by *Chaetomium perlucidum,* a new agent of cerebral phaeohyphomycosis. *J Clin Microbiol*. 2003;41:5302–5307.
67. Kanj SS, Amr SS, Roberts GD. *Ramichloridium mackenziei* brain abscess: report of two cases and review of the literature. *Med Mycol*. 2001;39:97–102.
68. Sutton DA, Slifkin M, Yakulis R, et al. U.S. case report of cerebral phaeohyphomycosis caused by *Ramichloridium obovoideum (R. mackenziei):* criteria for identification, therapy, and review of other known dematiaceous neurotropic taxa. *J Clin Microbiol*. 1998;36:708–715.
69. Surash S, Tyagi A, de Hoog GS, et al. Cerebral phaeohyphomycosis caused by *Fonsecaea monophora*. *Med Mycol*. 2005;43:465–472.
70. Engemann J, Kaye K, Cox G, et al. *Exophiala* infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July-November 2002. *Morb Mortal Wkly Rep*. 2002;51:1109–1112.
71. Kerkering TM, Grifasi ML, Baffoe-Bonnie AW, et al. Early clinical observations in prospectively followed patients with fungal meningitis related to contaminated epidural steroid injections. *Ann Intern Med*. 2013;158:154–161.
72. Ritter JM, Muehlenbachs A, Blau A. *Exserohilum* infections associated with contaminated steroid injections: a clinicopathologic review of 40 cases. *Immunopathol Infect Dis*. 2013;283:1–12.
73. Gade L, Scheel CM, Pham CD, et al. Detection of fungal DNA in human body fluids and tissues during a multistate outbreak of fungal meningitis and other infections. *Eukaryot Cell*. 2013;12:677–683.
74. Vallabhaneni S, Purfield AE, Benedict K, et al. Cardiothoracic surgical site phaeohyphomycosis caused by *Bipolaris* mould, multiple US states, 2008-2013: a clinical description. *Med Mycol*. 2016;54:318–321.
76. Washburn RG, Kennedy DW, Begley MG, et al. Chronic fungal sinusitis in apparently normal hosts. *Medicine (Baltimore)*. 1988;67:231–247.
77. Oliveira Ramos AM, Oliveira Sales A, Andrade MC, et al. A simple method for detecting subcutaneous phaeohyphomycosis with light colored fungi. *Am J Surg Pathol*. 1995;19:109–114.
78. Kimura M, McGinnis MR. Fontana-Masson-stained tissue from culture-proven mycoses. *Arch Pathol Lab Med*. 1998;122:1107–1111.
80. Whittle DI, Kominos S. Use of itraconazole for treating subcutaneous phaeohyphomycosis caused by *Exophiala jeanselmei*. *Clin Infect Dis*. 1995;21:1068.
81. Al-Abdely HM, Akkunaizi AM, Al-Tawfiq JA, et al. Successful therapy of cerebral phaeohyphomycosis due to *Ramichloridium mackenziei* with the new triazole posaconazole. *Med Mycol*. 2005;43:91–95.
82. Negroni R, Helou SH, Petri N, et al. Case study: posaconazole treatment of disseminated phaeohyphomycosis due to *Exophiala spinifera*. *Clin Infect Dis*. 2004;38:e15–e20.
83. Agger WA, Andes D, Burgess JW. *Exophiala jeanselmei* infection in a heart transplant recipient successfully treated with oral terbinafine. *Clin Infect Dis*. 2004;38:e112–e115.
84. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. *JAMA*. 2006;296:953–963.
85. Guilhermetti E, Takahachi G, Shinobu CS, et al. *Fusarium* spp. as agents of onychomycosis in immunocompetent hosts. *Int J Dermatol*. 2007;46:822–826.
86. Nucci M, Anaissie E. Cutaneous infection by *Fusarium* species in healthy and immunocompromised hosts: implications for diagnosis and management. *Clin Infect Dis*. 2002;35:909–920.
88. Wheeler MS, McGinnis MR, Schell WA, et al. *Fusarium* infection in burned patients. *Am J Clin Pathol*. 1981;75:304–311.
89. Testerman GM, Steagald MK, Colquitt LA, et al. Disseminated *Fusarium* infection in a multiple trauma patient. *South Med J*. 2008;101:320–323.
90. Strum AW, Grave W, Kwee WS. Disseminated *Fusarium oxysporum* infection in a patient with heat stroke. *Lancet*. 1989;1:968.
95. Ammari LK, Puck JM, McGowan KL. Catheter-related *Fusarium solani* fungemia and pulmonary infection in a patient with leukemia in remission. *Clin Infect Dis*. 1993;16:148–150.
96. Raad I, Hachem R. Treatment of central venous catheter-related fungemia due to *Fusarium oxysporum*. *Clin Infect Dis*. 1995;20:709–711.
97. Girmenia C, Arcese W, Micozzi A, et al. Onychomycosis as a possible origin of disseminated *Fusarium solani* infection in a patient with severe aplastic anemia. *Clin Infect Dis*. 1992;14:1167.
98. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic *Fusarium* species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. *Clin Infect Dis*. 2001;33:1871–1878.
99. Pires-Goncalves RH, Sartori FG, Montanari LB, et al. Occurrence of fungi in water used at a haemodialysis centre. *Lett Appl Microbiol*. 2008;46:542–547.
100. Krcméry V, Spanik S, Kunova A, et al. Breakthrough fungemia appearing during empiric therapy with amphotericin B. *Chemotherapy*. 1997;43:367–370.
101. Cudillo L, Girmenia C, Santilli S, et al. Breakthrough fusariosis in a patient with acute lymphoblastic leukemia receiving voriconazole prophylaxis. *Clin Infect Dis*. 2005;40:1212–1213.
102. Kim MS, Lee HM, Sung HS, et al. Breakthrough disseminated fusariosis in an immunocompromised patient on voriconazole therapy. *Int J Dermatol*. 2012;51:621–623.
103. Bose P, Parekh HD, Holter JL, et al. Disseminated fusariosis occurring in two patients despite posaconazole prophylaxis. *J Clin Microbiol*. 2011;49:1674.
104. Liu K, Howell DN, Perfect JR, et al. Morphologic criteria for the preliminary identification of *Fusarium, Paecilomyces,* and *Acremonium* species by histopathology. *Am J Clin Pathol*. 1998;109:45–54.
105. Nelson PE, Dignani MC, Anaissie EJ. Taxonomy, biology, and clinical aspects of *Fusarium* species. *Clin Microbiol Rev*. 1994;7:479–504.
106. van Diepeningen AD, Brankovics B, Iltes J, et al. Diagnosis of *Fusarium* infections: approaches to identification by the clinical mycology laboratory. *Curr Fungal Infect Rep*. 2015;9:135–143.
107. Tortorano AM, Esposto MC, Prigitano A, et al. Cross-reactivity of *Fusarium* spp. in the *Aspergillus galactomannan* enzyme-linked immunosorbent assay. *J Clin Microbiol*. 2012;50:1051–1053.
108. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with haematologic malignancies and *Fusarium* infection. *Cancer*. 2003;98:315–319.
109. Wolff MA, Ramphai R. Use of amphotericin B lipid complex for treatment of disseminated cutaneous *Fusarium* infection in a neutropenic patient. *Clin Infect Dis*. 1995;20:1568–1569.
110. Apostolidis J, Bouzani M, Platsouka E, et al. Resolution of fungemia due to *Fusarium* species in a patient with acute leukemia treated with caspofungin. *Clin Infect Dis*. 2003;36:1349–1350.
111. Neuburger S, Massenkeil G, Seibold M, et al. Successful salvage treatment of disseminated cutaneous fusariosis with liposomal amphotericin B and terbinafine after allogeneic stem cell transplantation. *Transpl Infect Dis*. 2008;10:290–293.
114. Cordoba S, Rodero L, Vivot W, et al. In vitro interactions of antifungal agents against clinical isolates of *Fusarium* spp. *Int J Antimicrob Agents*. 2008;31:171–174.
115. Clancy CJ, Nguyen MH. The combination of amphotericin B and azithromycin as a potential new therapeutic approach to fusariosis. *J Antimicrob Chemother*. 1998;41:127–130.
116. Ortoneda M, Capilla J, Pastor FJ, et al. Efficacy of liposomal amphotericin B in treatment of systemic murine fusariosis. *Antimicrob Agents Chemother*. 2002;46:2273–2275.
117. Lozano-Chiu M, Arikan S, Paetznick VL, et al. Treatment of murine fusariosis with SCH 56592. *Antimicrob Agents Chemother*. 1999;43:589–591.
118. Graybill JR, Najvar LK, Gonzalez GM, et al. Improving the mouse model for studying the efficacy of voriconazole. *J Antimicrob Chemother*. 2003;51:1373–1376.
120. Spielberger RT, Falleroni MJ, Coene AJ, et al. Concomitant amphotericin B therapy, granulocyte transfusions, and GM-CSF administration for disseminated infection with *Fusarium* in a granulocytopenic patient. *Clin Infect Dis*. 1993;16:528–530.
125. Kratzer C, Tobudic S, Schmoll M, et al. *In vitro* activity and synergism of amphotericin B, azoles, and cationic antimicrobials against the emerging pathogen *Trichoderma* spp. *J Antimicrob Chemother*. 2006;58:1058–1061.
128. Iwen PC, Schutte SD, Florescu DF, et al. Invasive *Scopulariopsis brevicaulis* infection in an immunocompromised patient and review of prior cases caused by *Scopulariopsis* and *Microascus* species. *Med Mycol*. 2012;50:561–569.
130. Gueho E, Improvisi L, de Hoog GS, et al. *Trichosporon* in humans, a practical account. *Mycoses*. 1994;37:3–10.
131. Sugita T, Nishikawa A, Shinoda T. Identification of *Trichosporon asahii* by PCR based on sequences of the internal transcribed spacer regions. *J Clin Microbiol*. 1998;36:2742–2744.
132. Sugita T, Nishikawa A, Shinoda T, et al. Taxonomic position of deep-seated, mucosa associated, and superficial isolates of *Trichosporon cutaneum* from trichosporonosis patients. *J Clin Microbiol*. 1995;33:1368–1370.
133. Itoh T, Hosokawa H, Kohdera U, et al. Disseminated infection with *Trichosporon asahii*. *Mycoses*. 1996;39:195–199.
134. Dabas Y, Xess I, Kale P. Molecular and antifungal susceptibility study of trichosporonemia and emergence of *Trichosporon mycotoxinivorans* as a bloodstream pathogen. *Med Mycol*. 2017;55:518–527.
135. Haupt HM, Merz WG, Beschorner WE, et al. Colonization and infection with *Trichosporon* species in the immunosuppressed host. *J Infect Dis*. 1983;147:199–203.
136. Hung CC, Chang SC, Chen YC, et al. *Trichosporon beigelii* fungemia in patients with acute leukemia: report of three cases. *J Formos Med Assoc*. 1995;94:127–131.
137. Hajjeh RA, Blumberg HM. Bloodstream infection due to *Trichosporon beigelii* in a burn patient: case report and review of therapy. *Clin Infect Dis*. 1995;20:913–916.
138. Mirza SH. Disseminated *Trichosporon beigelii* infection causing skin lesions in a renal transplant patient. *J Infect*. 1993;27:67–70.
139. Nahass GT, Rosenberg SP, Leonardi CL, et al. Disseminated infection with *Trichosporon beigelii*. *Arch Dermatol*. 1993;129:1020–1023.
140. Walsh TJ, Newman KR, Moody M, et al. Trichosporonosis in patients with neoplastic disease. *Medicine (Baltimore)*. 1986;65:268–279.

141. Yong L, Hartmann T, Tao Z, et al. Breakthrough trichosporonosis in patients receiving echinocandins: case report and literature review. *Chin Med J*. 2012;125:2632–2635.
142. Hazirolan G, Canton E, Sahin S, et al. Head-to-head comparison of inhibitory and fungicidal activities of fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole against clinical isolates of *Trichosporon asahii*. *Antimicrob Agents Chemother*. 2013;57:4841–4847.
143. Chitasombat MN, Kofteridis DP, Jiang Y, et al. Rare opportunistic non-*Candida,* non-*Cryptococcus*) yeast bloodstream infections in patients with cancer. *J Infect*. 2012;64:68–75.
144. Dankner WM, Spector SA, Fierer J, et al. *Malassezia* fungemia in neonates and adults: complication of hyperalimentation. *Rev Infect Dis*. 1987;9:743–753.
145. Barber GR, Brown AE, Kiehn TE, et al. Catheter-related *Malassezia furfur* fungemia in immunocompromised patients. *Am J Med*. 1993;95:365–370.
146. Brooks R, Brown L. Systemic infections with *Malassezia furfur* in an adult receiving long-term hyperalimentation therapy. *J Infect Dis*. 1987;156:410–411.
147. Boekhout T, Kamp M, Geuho E. Molecular typing of *Malassezia* species with PFGE and RAPD. *Mol Mycol*. 1998;36:365–372.
148. Chang HJ, Miller HL, Watkins N, et al. An epidemic of *Malassezia pachydermatis* in an intensive care nursery associated with colonization of health care workers' pet dogs. *N Engl J Med*. 1998;338:706–711.
149. Powell DA, Marcon MJ. Failure to eradicate *Malassezia furfur* broviac catheter infection with antifungal therapy. *Pediatr Infect Dis J*. 1987;6:579–588.
151. Marcon MJ, Durreil DE, Powell DA, et al. In vitro activity of systemic antifungal agents against *Malassezia furfur*. *Antimicrob Agents Chemother*. 1987;31:951–953.
152. Perez-Sanchez I, Anguita J, Martin-Rabadan P, et al. *Blastoschizomyces capitatus* infection in acute leukemia patients. *Leuk Lymphoma*. 2000;39:209–212.
153. Martino R, Salavert M, Parody R, et al. *Blastoschizomyces capitatus* infection in patients with leukemia: report of 26 cases. *Clin Infect Dis*. 2004;38:335–341.
156. Sanz MA, Lopez FA, Martinez ML, et al. Disseminated *Blastoschizomyces capitatus* infection in acute myeloblastic leukemia. *Support Care Cancer*. 1996;4:291–293.
157. Serena C, Marine M, Marimon R, et al. Effect of antifungal treatment in a murine model of blastoschizomycosis. *Int J Antimicrob Agents*. 2007;29:79–83.
158. Desnos-Ollivier M, Blanc C, Garcia-Hermoso D, et al. Misidentification of *Saprochaeta clavata* as *Magnusiomyces capitatus* in clinical isolates: utility of internal transcribed spacer sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometery and importance of reliable databases. *J Clin Microbiol*. 2014;52:2196–2198.
159. Vaux S, Criscuolo A, Desnos-Ollivier M, et al. Multicenter outbreak of infections causes by *Saprochaeta clavata,* an unrecognized opportunistic fungal pathogen. *MBio*. 2014;5:2309–2314.
161. Fernadez-Ruiz M, Guinea J, Puig-Asensio M, et al. Fungemia due to rare opportunistic yeasts: data from a population-based surveillance in Spain. *Med Mycol*. 2017;55:125–136.
162. da Matta VLR, Melhem MC, Colombo AL, et al. Antifungal drug susceptibility profile of *Pichia anomala* isolates from patients presenting with nosocomial fungemia. *Antimicrob Agents Chemother*. 2007;51:1573–1576.
163. Thuler LC, Faivichenco S, Velasco E, et al. Fungaemia caused by *Hansenula anomala*—an outbreak in a cancer hospital. *Mycoses*. 1997;40:193–196.
164. Zaas AK, Boyce M, Schell W, et al. Risk of fungemia due to *Rhodotorula* and antifungal susceptibility testing of *Rhodotorula* isolates. *J Clin Microbiol*. 2003;41:5233–5235.
165. Nunes JM, Bizerra FC, Ferreira RC, et al. Molecular identification, antifungal susceptibility profile, and biofilm formation of clinical and environmental *Rhodotorula* species isolates. *Antimicrob Agents Chemother*. 2013;57:382–389.
166. Munoz P, Bouza E, Cuenca-Estrella M, et al. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. *Clin Infect Dis*. 2005;40:1625–1634.
167. DiSalvo AF, Fielding AM, Ajello L. Infection caused by *Penicillium marneffei:* description of first natural infection in man. *Am J Clin Pathol*. 1973;59:259–263.
168. Segretain G. *Penicillium marneffei* n. sp., agent d'une mycose du système réticulo-endothélial. *Mycopathol Mycol Appl*. 1959;11:327–353.
169. Vanittanakom N, Cooper CR, Fisher MC, et al. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev*. 2006;19:95–110.
173. Hung C, Hsueh P, Chen M, et al. Invasive infection caused by *Penicillium marneffei:* an emerging pathogen in Taiwan. *Clin Infect Dis*. 1998;26:202–203.
174. Kwan EYW, Lau YL, Yuen KY, et al. *Penicillium marneffei* infection in a non-HIV infected child. *J Paediatr Child Health*. 1997;33:267–271.
175. Sirisanthana V, Sirisanthana T. *Penicillium marneffei* infection in children infected with human immunodeficiency virus. *Pediatr Infect Dis J*. 1993;12:1021–1025.
176. Ajello L, Padhye AA, Sukroongreung S, et al. Occurrence of *Penicillium marneffei* infections among wild bamboo rats in Thailand. *Mycopathologia*. 1995;131:1–8.
177. Cooper CR. From bamboo rats to humans: the odyssey of *Penicillium marneffei*. *ASM News*. 1998;64:390–396.
178. Chariyalertsak S, Vanittanakom P, Nelson KE, et al. *Rhizomys sumatrensis* and *Cannomys badius,* new natural animal hosts of *Penicillium marneffei*. *J Med Vet Mycol*. 1996;34:105–110.
179. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, et al. Case-control study of the risk factors for *Penicillium marneffei* infection in human immunodeficiency virus–infected patients in northern Thailand. *Clin Infect Dis*. 1997;24:1080–1086.
180. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, et al. Seasonal variation of disseminated *Penicillium marneffei* infections in northern Thailand: a clue to the reservoir? *J Infect Dis*. 1996;173:1490–1493.
183. Ko CI, Hung CC, Chen MY, et al. Endoscopic diagnosis of intestinal penicilliosis marneffei: report of three cases and review of the literature. *Gastrointest Endosc*. 1999;50:111–114.
184. Wortmann PD. Infection with *Penicillium marneffei*. *Int J Dermatol*. 1996;35:393–399.
185. Cheng NC, Won WW, Fung CP, et al. Unusual pulmonary manifestations of disseminated *Penicillium marneffei* infection in three AIDS patients. *Med Mycol*. 1998;36:429–432.
186. Deng Z, Ribas JL, Gibson DW, et al. Infections caused by *Penicillium marneffei* in China and southeast Asia: review of eighteen published cases and report of four more Chinese cases. *Rev Infect Dis*. 1988;10:640–652.
187. Le T, Chi NH, Cuc NTK, et al. AIDS-associated *Penicillium marneffei* infection of the central nervous system. *Clin Infect Dis*. 2010;51:1458–1462.
188. Hilmarsdottir I, Coutellier A, Elbaz J, et al. A French case of laboratory-acquired disseminated *Penicillium marneffei* infection in a patient with AIDS. *Clin Infect Dis*. 1994;19: 357–358.
189. Jones PD, See J. *Penicillium marneffei* infection in patients infected with human immunodeficiency virus: late presentation in an area of nonendemicity. *Clin Infect Dis*. 1992;15:744.
190. Supparatpinyo K, Sirisanthana T. Disseminated *Penicillium marneffei* infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. *Clin Infect Dis*. 1994;18:246–247.
191. Cooper CR, McGinnis MR. Pathology of *Penicillium marneffei:* an emerging acquired immunodeficiency syndrome-related pathogen. *Arch Pathol Lab Med*. 1997;121:798–804.
192. Chaiyaroj SC, Chawengkirttikul R, Sirisinha S, et al. Antigen detection assay for identification of *Penicillium marneffei* infection. *J Clin Microbiol*. 2003;41:432–434.
193. Desakorn V, Simpson AJH, Wuthiekanun V, et al. Development and evaluation of rapid urinary antigen detection tests for diagnosis of *Penicillium marneffei*. *J Clin Microbiol*. 2002;40:3179–3183.
194. Huang Y, Hung C, Liao C, et al. Detection of circulating galactomannan in serum samples for diagnosis of *Penicillium marneffei* infection and cryptococcosis among patients infected with human immunodeficiency virus. *J Clin Microbiol*. 2007;45:2858–2862.
197. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic *Penicillium marneffei* infections in AIDS patients. *Am J Trop Med Hyg*. 2007;77:350–353.
198. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus–infected patients with disseminated *Penicillium marneffei* infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother*. 1993;37:2407–2411.
201. Sudjaritruk T, Sirisanthana T, Sirisanthana V. Immune reconstitution inflammatory syndrome from *Penicillium marneffei* in an HIV-infected child: a case report and review of literature. *BMC Infect Dis*. 2012;12:1–6.
203. Taborda PR, Taborda VA, McGinnis MR. *Lacazia loboi* gen. nov., comb, nov., the etiologic agent of lobomycosis. *J Clin Microbiol*. 1999;37:2031–2033.
204. Burns RA, Roy JS, Woods C, et al. Report of the first human case of lobomycosis in the United States. *J Clin Microbiol*. 2000;38:1283–1285.
205. Al-Daraji WI, Husain E, Robson A. Lobomycosis in African patients. *Br J Dermatol*. 2008;159:234–236.
206. Papadavid E, Dalamaga M, Kapniari I, et al. Lobomycosis: a case from Southeastern Europe and review of the literature. *J Dermatol Case Rep*. 2012;6:65–69.
207. Elsayed S, Kuhn SM, Barber D, et al. Human case of lobomycosis. *Emerg Infect Dis*. 2004;10:715–718.
208. Bustamante B, Seas C, Salomon M, et al. Lobomycosis successfully treated with posaconazole. *Am J Trop Med Hyg*. 2013;88:1207–1208.
209. Anstead GM, Sutton DA, Graybill JR. Adiaspiromycosis causing respiratory failure and a review of human infections due to *Emmonsia* and *Chrysosporium* spp. *J Clin Microbiol*. 2012;50:1346–1354.
210. Mendes MO, Moraes MAP, Renoiner EIM. Acute conjunctivitis with episcleritis and anterior uveitis linked to adiaspiromycosis and freshwater sponges, amazon region, Brazil, 2005. *Emerg Infect Dis*. 2009;15:633–639.
211. Schwartz IS, Kenyon C, Feng P, et al. 50 years of *Emmonsia* disease in humans: the dramatic emergence of a cluster of novel fungal pathogens. *PLoS Pathog*. 2015;11:e1005198.
212. Dot JM, Debourogogne A, Champigneulle J, et al. Molecular diagnosis of disseminated adiaspiromycosis due to *Emmonsia crescens*. *J Clin Microbiol*. 2009;47:1269–1273.
216. Dukik K, Munoz JF, Jiang Y, et al. Novel taxa of thermally dimorphic systemic pathogens in the ajellomycetaceae (Onygenales). *Mycoses*. 2017;60:296–309.
217. Schwartz IS, Lerm B, Hoving JC, et al. *Emergomyces africanus* in soil, South Africa. *Emerg Infect Dis*. 2018;24:377–380.
218. Maphanga TG, Britz E, Zulu TG, et al. In vitro antifungal susceptibility of yeast and mold phases of isolates of dimorphic fungal pathogen *Emergomyces africanus* (formerly *Emmonsia* sp.) from HIV-infected South African patients. *J Clin Microbiol*. 2017;55:1812–1820.
219. Rofael M, Schwartz IS, Sigler L, et al. *Emmonsia helica* infection in HIV-infected man, California, USA. *Emerg Infect Dis*. 2018;24:166–168.
220. Wang P, Kenyon C, de Hoog S, et al. A novel dimorphic pathogen, *Emergomyces orientalis* (Onygenales), agent of disseminated infection. *Mycoses*. 2017;60:310–319.
221. Schwartz IS, Sanche S, Wiederhold NP, et al. *Emergomyces canadensis,* a dimorphic fungus causing fatal systemic human disease in North America. *Emerg Infect Dis*. 2018;24:758–761.
222. Rosario MI, Roman FL, Batista AM, et al. Pigeons and their droppings as reservoirs of *Candida* and other zoonotic yeasts. *Rev Iberoam Micol*. 2017;34:211–214.
224. Krcméry V Jr. Systemic chlorellosis, an emerging infection in humans caused by algae. *Int J Antimicrob Agents*. 2000;15:235–237.
225. Masuda M, Hirose N, Ishikawa T, et al. *Prototheca miyajii* sp. nov., isolated from a patient with systemic protothecosis. *Int J Syst Evol Microbiol*. 2016;66:1510–1520.
226. Kim ST, Suh KS, Chae YS, et al. Successful treatment with fluconazole of protothecosis at the site of an intralesional corticosteroid injection. *Br J Dermatol*. 1996;135:803–806.
227. Carey WP, Kaykova Y, Bandres JC, et al. Cutaneous protothecosis in a patient with AIDS and severe functional defect: successful therapy with amphotericin B. *Clin Infect Dis*. 1997;25:1265–1266.
228. Polk P, Sanders DY. Cutaneous protothecosis in association with the acquired immunodeficiency syndrome. *South Med J*. 1997;90:831–832.
229. Narita M, Muder RR, Cacciarelli TV, et al. Protothecosis after liver transplantation. *Liver Transpl*. 2008;14:1211–1215.
230. Ahn A, Choe Y, Chang J, et al. Chronic eosinophilic meningoencephalitis by *Prototheca wickerhamii* in an immunocompetent boy. *Pediatr Infect Dis J*. 2017;36:687–689.
231. Matsumoto Y, Shibata M, Adachi A, et al. Two cases of protothecosis in Nagoya, Japan. *Australas J Dermatol*. 1996;37:S42–S43.
232. Tang WY, Lo KK, Lam WY, et al. Cutaneous protothecosis: report of a case in Hong Kong. *Br J Dermatol*. 1995;133:479–482.
233. Okuyama Y, Hamaguchi T, Teramoto T, et al. A human case of protothecosis successfully treated with itraconazole. *Nippon Ishinkin Gakkai Zasshi*. 2001;42:143–147.
234. Yun CH, Jeong JH, Ryu HR, et al. Cutaneous protothecosis responds rapidly to voriconazole. *Int J Dermatol*. 2016;55:1373–1377.
235. Gaastra WM, Lipman LJA, de Cock AWAM, et al. *Phythium insidiosum*: an overview. *Vet Microbiol*. 2010;148:1–18.
237. Lelievre L, Borderie V, Garcia-Hermoso D, et al. Case report: imported *Pythium insidiosum* keratitis after a

swim in Thailand by a contact-wearing traveler. *Am J Trop Med Hyg*. 2015;92:270–273.
238. Franco DM, Aronson JF, Hawkins HK, et al. Systemic *Pythium insidiosum* in a pediatric burn patient. *Burns*. 2010;36:e68–e71.
239. Sudjaritruk T, Sirisanthana V. Successful treatment of a child with vascular pythiosis. *BMC Infect Dis*. 2011;11:33–36.
240. Calvano TP, Blatz PJ, Vento TJ, et al. *Pythium aphanidermatum* infection following combat trauma. *J Clin Microbiol*. 2011;49:3710–3713.
241. Evriviades D, Jeffery S, Cubison T, et al. Shaping the military wound: issues surrounding the reconstruction of injured servicemen at the royal centre for defence medicine. *Phil Trans R Soc B*. 2011;366:219–230.
243. Salipante SJ, Hoogestraat DR, SenGupta DJ, et al. Molecular diagnosis of subcutaneous *Pythium insidiosum* infection by use of PCR screening and DNA sequencing. *J Clin Microbiol*. 2012;50:1480–1483.
245. Jesus FPK, Ferreiro L, Loreta ES, et al. In vitro synergism observed with azithromycin, clarithromycin, minocycline, or tigecycline in association with antifungal agents against *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2014;58:5621–5625.
246. Loreto ES, Tondolo JSM, Pilotto MB, et al. New insights into the in vitro susceptibility of *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2014;58:7534–7537.
247. Mahl DL, de Jesus FPK, Loreto ES, et al. *In vitro* susceptibility of *Pythium insidiosum* isolates to aminoglycoside antibiotics and tigecycline. *Antimicrob Agents Chemother*. 2012;56:4021–4023.
248. Itaqui SR, Verdi CM, Tondolo JSM, et al. In vitro synergism between azithromycin or terbinafine and topical antimicrobial agents against *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2016;60:5023–5025.
249. Jesus FPK, Loreto ES, Ferreiro L, et al. In vitro and in vivo antimicrobial activities of minocycline in combination with azithromycin, clarithromycin, or tigecycline against *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2016;60:87–91.
251. Herr RA, Ajello L, Taylor JW, et al. Phylogenetic analysis of *Rhinosporidium seeberi*'s 18S small-subunit ribosomal DNA groups this pathogen among members of the protoctistan *Mesomycetozoa* clade. *J Clin Microbiol*. 1999;37:2750–2754.
252. Vilela R, Mendoza L. The taxonomy and phylogenetics of the human and animal pathogen *Rhinosporidium seeberi:* a critical review. *Rev Iberoam Micol*. 2012;29:185–199.
253. Sudarshan V, Goel NK, Gahine R, et al. Rhinosporidiosis in raipur, chhattisgarh: a report of 462 cases. *Indian J Pathol Microbiol*. 2007;50:718–721.
254. Dutta S, Haldar D, Dutta M, et al. Socio-demographic correlates of rhinosporidiosis: a hospital-based epidemiologic study in Purulia, India. *Indian J otolaryngol Head Neck Surg*. 2017;69:108–112.
255. Karthikeyan P, Vijayasundaram S, Pulimoottil DT. A retrospective epidemiological study of rhinosporidiosis in a rural tertiary care centre in Pondicherry. *J Clin Diagn Res*. 2016;10:MC4–MC8.
256. Lasser A, Smith HW. Rhinosporidiosis. *Arch Otolaryngol*. 1976;102:308–310.
257. Reidy JJ, Sudesh S, Klafter AB, et al. Infection of the conjunctiva by *Rhinosporidium seeberi*. *Surv Ophthalmol*. 1997;41:409–413.
258. Snidvongs ML, Supanakorn S, Supiyaphun P. Severe epistaxis from rhinosporidiosis: a case report. *J Med Assoc Thai*. 1998;81:555–558.
259. Thappa DM, Venkatesan S, Sirka CS, et al. Disseminated cutaneous rhinosporidiosis. *J Dermatol*. 1998;25:527–532.

References

1. Chen M, Zeng J, De Hoog GS, et al. The "species complex" issue in clinically relevant fungi: a case study in *Scedosporium apiospermum*. *Fungal Biol*. 2016;120:137–146.
2. Lackner M, de Hoog GS, Verweij PE, et al. Species-specific antifungal susceptibility patterns of *Scedosporium* and *Pseudallescheria* species. *Antimicrob Agents Chemother*. 2012;56:2635–2642.
3. Guarro J, Kantarcioglu AS, Horre R, et al. *Scedosporium apiospermum:* changing clinical spectrum of a therapy-refractory opportunist. *Med Mycol*. 2006;44:295–327.
4. Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by *Scedosporium* spp. *Clin Microbiol Rev*. 2008;21:157–197.
5. Kantarcioglu AS, Guarro J, de Hoog GS. Central nervous system infections by members of the *Pseudallescheria boydii* species complex in healthy and immunocompromised hosts: epidemiology, clinical characteristics and outcome. *Mycoses*. 2008;51:275–290.
6. Kantarcioglu AS, de Hoog GS, Guarro J. Clinical characteristics and epidemiology of pulmonary pseudallescheriasis. *Rev Iberoam Micol*. 2012;29:1–13.
7. Miller MA, Greenberger PA, Amerian R, et al. Allergic bronchopulmonary mycosis caused by *Pseudallescheria boydii*. *Am Rev Respir Dis*. 1993;148:810–812.
8. Bates DD, Mims JW. Invasive fungal sinusitis caused by *Pseudallescheria boydii:* case report and literature review. *Ear Nose Throat J*. 2006;85:729–737.
9. Husain S, Munoz P, Forrest G, et al. Infections due to *Scedosporium apiospermum* and *Scedosporium prolificans* in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. *Clin Infect Dis*. 2005;40:89–99.
10. Lamris GA, Chamilos G, Lewis RE, et al. *Scedosporium* infection in a tertiary care cancer center: a review of 25 cases from 1989-2006. *Clin Infect Dis*. 2006;43:1580–1584.
11. Castiglioni B, Dutton DA, Rinaldi MG, et al. *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*): infection in solid organ transplant recipients in a tertiary medical center and review of the literature. *Medicine (Baltimore)*. 2002;81:333–348.
12. Bernstein EF, Schuster MG, Stieritz DD, et al. Disseminated cutaneous *Pseudallescheria boydii*. *Br J Dermatol*. 1995;132:456–460.
13. Larocco A, Barron JB. Endogenous *Scedosporium apiospermum* endophthalmitis. *Retina*. 2005;25:1090–1093.
14. Hung CC, Chang SC, Yang PC, et al. Invasive pulmonary pseudallescheriasis with direct invasion of the thoracic spine in an immunocompetent patient. *Eur J Clin Microbiol Infect Dis*. 1994;13:749–751.
15. Halpern AA, Nagel DA, Schurman DJ. *Allescheria boydii* osteomyelitis following multiple steroid injections and surgery. *Clin Orthop*. 1977;126:232–234.
16. Lavy D, Morin O, Venet G, et al. *Pseudallescheria boydii* knee arthritis in a young immunocompetent adult two years after a compound patellar fracture. *Joint Bone Spine*. 2001;68:517–520.
17. Tirado-Miranda R, Solera-Santos J, Brasero JC, et al. Septic arthritis due to *Scedosporium apiospermum:* case report and review. *J Infect*. 2001;43:210–212.
18. Montero A, Cohen JE, Fernandez MA, et al. Cerebral pseudallescheriasis due to *Pseudallescheria boydii* as the first manifestation of AIDS. *Clin Infect Dis*. 1998;26:1476–1477.
19. Bryan CS, DiSalvo AF, Kaufman L, et al. *Petriellidium boydii* infection of the sphenoid sinus. *Am J Clin Pathol*. 1980;74:846–851.
20. Dworzack DL, Clark RB, Borkowski WJ, et al. *Pseudallescheria boydii* brain abscess: association with near-drowning and efficacy of high-dose, prolonged miconazole therapy in patients with multiple abscesses. *Medicine (Baltimore)*. 1989;68:218–224.
21. Benham RW, Georg LK. *Allescheria boydii,* causative agent in a case of meningitis. *J Invest Dermatol*. 1948;10:99–110.
22. Fernandez-Flores A, Lopez-Medrano R, Fuster-Foz C. Histopathological clues in the diagnosis of fungal infection by *Scedosporium* in a case of endophthalmitis starting as conjunctivitis. *J Cutan Pathol*. 2016;43:461–467.
23. Galgiani JN, Stevens DA, Graybill JR, et al. *Pseudallescheria boydii* infections treated with ketoconazole: clinical evaluations of seven patients and in vitro susceptibility results. *Chest*. 1984;82:219–224.
24. Piper JP, Golden J, Brown D, et al. Successful treatment of *Scedosporium apiospermum* suppurative arthritis with itraconazole. *Pediatr Infect Dis J*. 1990;9:674–675.
25. Barbaric D, Shaw PJ. *Scedosporium* infection in immunocompromised patients: successful use of liposomal amphotericin B and itraconazole. *Med Pediatr Oncol*. 2001;37:122–125.
26. Gonzalez GM. *In vitro* activities of isavuconazole against opportunistic filamentous and dimorphic fungi. *Med Mycol*. 2009;47:71–76.
27. Carrillo AJ, Guarro J. In vitro activities of four novel triazoles against *Scedosporium* spp. *Antimicrob Agents Chemother*. 2001;45:2151–2153.
28. Troke P, Aguirrebengoa K, Arteaga C, et al. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. *Antimicrob Agents Chemother*. 2008;52:1743–1750.
29. Nesky MA, McDougal EC, Peacock JE Jr. *Pseudallescheria boydii* brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. *Clin Infect Dis*. 2000;31:673–677.
30. Poza G, Montoya J, Redondo C, et al. Meningitis caused by *Pseudallescheria boydii* treated with voriconazole. *Clin Infect Dis*. 2000;30:981–982.
31. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. *Clin Microbiol Infect*. 2014;20:27–46.
32. Mellinghoff IK, Winston DJ, Mukwaya G, et al. Treatment of *Scedosporium apiospermum* brain abscesses with posaconazole. *Clin Infect Dis*. 2002;34:1648–1650.
33. Malloch D, Salkin IF. A new species of *Scedosporium* associated with osteomyelitis in humans. *Mycotaxon*. 1984;21:247–255.
34. Rodriguez-Tudela JL, Berenguer J, Guarro J, et al. Epidemiology and outcome of *Scedosporium prolificans* infection: a review of 162 cases. *Med Mycol*. 2009;47:359–370.
35. Wilson CM, O'Rourke EJ, McGinnis MR, et al. *Scedosporium inflatum:* clinical spectrum of a newly recognized pathogen. *J Infect Dis*. 1990;161:102–107.
36. Wood GM, McCormack JG, Muir DB, et al. Clinical features of human infection with *Scedosporium inflatum*. *Clin Infect Dis*. 1992;14:1027–1033.
37. Alvarez M, Ponga BL, Rayon C, et al. Nosocomial outbreak caused by *Scedosporium prolificans (inflatum):* four fatal cases in leukemia patients. *J Clin Microbiol*. 1995;33:3290–3295.
38. Bouza E, Munoz P, Vega L, et al. Clinical resolution of *Scedosporium prolificans* fungemia associated with reversal of neutropenia following administration of granulocyte colony-stimulating factor. *Clin Infect Dis*. 1996;23:192–193.
39. Kelly M, Stevens R, Konecny P. *Lomentospora prolificans* endocarditis – case report and literature review. *BMC Infect Dis*. 2016;16:36.
40. Farag SS, Firkin FC, Andrew JH, et al. Fatal disseminated *Scedosporium inflatum* infection in a neutropenic immunocompromised patient. *J Infect*. 1992;25:201–204.
41. Rabodonirina M, Paulus S, Thevenet F, et al. Disseminated *Scedosporium prolificans (S. inflatum)* infection after single-lung transplantation. *Clin Infect Dis*. 1994;19:138–142.
42. Madrigal V, Alonso J, Bureo E, et al. Fatal meningoencephalitis caused by *Scedosporium inflatum (Scedosporium prolificans)* in a child with lymphoblastic leukemia. *Eur J Clin Microbiol Infect Dis*. 1995;14:601–603.
43. Parize P, Boussaud V, Poinsignon V, et al. Clinical outcome of cystic fibrosis patients colonized by *Scedosporium* species following lung transplantation: a single-center 15-year experience. *Transpl Infect Dis*. 2017;19:e12738.
44. Schwarz C, Brandt C, Antweiler E, et al. Prospective multicenter German study on pulmonary colonization with *Scedosporium/Lomentospora* species in cystic fibrosis: epidemiology and new association factors. *PLoS ONE*. 2017;12:e0171485.
45. del Palacio A, Garau M, Amor E, et al. Case reports. Transient colonization with *Scedosporium prolificans:* report of four cases in Madrid. *Mycoses*. 2001;44:321–325.
46. Hopwood V, Evans EGV, Matthews J, et al. *Scedosporium prolificans,* a multi-resistant fungus, from a UK AIDS patient. *J Infect*. 1995;30:153–155.
47. Salkin IF, McGinnis MR, Dykstra MJ, et al. *Scedosporium inflatum,* an emerging pathogen. *J Clin Microbiol*. 1988;26:498–503.
48. Lennon PA, Cooper CR Jr, Salkin IF, et al. Ribosomal DNA internal transcribed spacer analysis supports synonomy of *Scedosporium inflatum* and *Lomentospora prolificans*. *Clin Microbiol*. 1994;32:2413–2416.
49. Ortoneda M, Capilla J, Pujol I, et al. Liposomal amphotericin B and granulocyte colony-stimulating factor therapy in a murine model of invasive infection by *Scedosporium prolificans*. *J Antimicrob Chemother*. 2002;49:525–529.
50. Capilla J, Yustes C, Mayayo E, et al. Efficacy of albaconazole (UR-9825) in treatment of disseminated *Scedosporium prolificans* infection in rabbits. *Antimicrob Agents Chemother*. 2003;47:1948–1951.
51. Afeltra J, Dannaoui E, Meis JF, et al. In vitro synergistic interaction between amphotericin B and pentamidine against *Scedosporium prolificans*. *Antimicrob Agents Chemother*. 2002;46:3323–3326.
52. Meletiadis J, Mouton JW, Meis JF, et al. In vitro drug interaction modeling of combinations of azoles with terbinafine against clinical *Scedosporium prolificans* isolates. *Antimicrob Agents Chemother*. 2003;47:106–117.
53. Meletiadis J, Mouton JW, Rodriguez-Tudela JL, et al. In vitro interaction of terbinafine with itraconazole against clinical isolates of *Scedosporium prolificans*. *Antimicrob Agents Chemother*. 2000;44:470–472.
54. Tong SYC, Peleg AY, Yoong J, et al. Breakthrough *Scedosporium prolificans* infection while receiving voriconazole prophylaxis in an allogeneic stem cell transplant recipient. *Transpl Infect Dis*. 2007;9:241–243.
55. Howden BP, Slavin MA, Schwarer AP, et al. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. *Eur J Clin Microbiol Infect Dis*. 2003;22:111–113.
56. Revankar SG, Sutton DA. Melanized fungi in human disease. *Clin Microbiol Rev*. 2010;23:884–928.
57. Nucci M, Akiti T, Barreiros G, et al. Nosocomial fungemia due to *Exophiala jeanselmei* var. *jeanselmei* and a *Rhinocladiella* species: newly described causes of bloodstream infection. *J Clin Microbiol*. 2001;39:514–518.
58. Revankar SG, Patterson JE, Sutton DA, et al. Disseminated phaeohyphomycosis: review of an emerging mycosis. *Clin Infect Dis*. 2002;34:467–476.
59. Jeon SJ, Nguyen TTT, Lee HB. Phylogenetic status of an unrecorded species of *Curvularia, C. spicifera,* based on current classification system of *Curvularia* and *Bipolaris* group using multi loci. *Microbiology*. 2015;43:210–217.
60. Rossman SNB, Cernoch PL, Davis JR. Dematiaceous fungi are an increasing cause of human disease. *Clin Infect Dis*. 1996;22:73–80.
61. Revankar SG, Sutton DA, Rinaldi MG. Primary central nervous system phaeohyphomycosis: a review of 101 cases. *Clin Infect Dis*. 2004;38:206–216.
62. Aldape KD, Fox HS, Roberts JP, et al. *Cladosporium trichoides* cerebral phaeohyphomycosis in a liver transplant recipient. *Am J Clin Pathol*. 1991;95:499–502.
63. Filizzola MJ, Martinez F, Rauf SJ. Phaeohyphomycosis of the central nervous system in immunocompetent hosts: report of a case and review of the literature. *Int J Infect Dis*. 2003;7:282–286.
64. Buxi TBS, Prakash K, Vohra R, et al. Imaging in phaeohyphomycosis of the brain. Case report. *Neuroradiology*. 1996;38:139–141.
65. Walz R, Bianchin M, Chaves ML, et al. Cerebral phaeohyphomycosis caused by *Cladophialophora bantiana* in a Brazilian drug abuser. *J Med Vet Mycol*. 1997;35:427–431.
66. Barron MA, Sutton DA, Veve R, et al. Invasive mycotic infections caused by *Chaetomium perlucidum,* a new agent of cerebral phaeohyphomycosis. *J Clin Microbiol*. 2003;41:5302–5307.
67. Kanj SS, Amr SS, Roberts GD. *Ramichloridium mackenziei* brain abscess: report of two cases and review of the literature. *Med Mycol*. 2001;39:97–102.
68. Sutton DA, Slifkin M, Yakulis R, et al. U.S. case report of cerebral phaeohyphomycosis caused by *Ramichloridium obovoideum (R. mackenziei):* criteria for identification, therapy, and review of other known dematiaceous neurotropic taxa. *J Clin Microbiol*. 1998;36:708–715.
69. Surash S, Tyagi A, de Hoog GS, et al. Cerebral phaeohyphomycosis caused by *Fonsecaea monophora*. *Med Mycol*. 2005;43:465–472.
70. Engemann J, Kaye K, Cox G, et al. *Exophiala* infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July-November 2002. *Morb Mortal Wkly Rep*. 2002;51:1109–1112.
71. Kerkering TM, Grifasi ML, Baffoe-Bonnie AW, et al. Early clinical observations in prospectively followed patients with fungal meningitis related to contaminated epidural steroid injections. *Ann Intern Med*. 2013;158:154–161.
72. Ritter JM, Muehlenbachs A, Blau A. *Exserohilum* infections associated with contaminated steroid injections: a clinicopathologic review of 40 cases. *Immunopathol Infect Dis*. 2013;283:1–12.
73. Gade L, Scheel CM, Pham CD, et al. Detection of fungal DNA in human body fluids and tissues during a multistate outbreak of fungal meningitis and other infections. *Eukaryot Cell*. 2013;12:677–683.
74. Vallabhaneni S, Purfield AE, Benedict K, et al. Cardiothoracic surgical site phaeohyphomycosis caused by *Bipolaris* mould, multiple US states, 2008-2013: a clinical description. *Med Mycol*. 2016;54:318–321.

75. deShazo RD, Chapin K, Swain RE. Fungal sinusitis. *N Engl J Med*. 1997;337:254–259.
76. Washburn RG, Kennedy DW, Begley MG, et al. Chronic fungal sinusitis in apparently normal hosts. *Medicine (Baltimore)*. 1988;67:231–247.
77. Oliveira Ramos AM, Oliveira Sales A, Andrade MC, et al. A simple method for detecting subcutaneous phaeohyphomycosis with light colored fungi. *Am J Surg Pathol*. 1995;19:109–114.
78. Kimura M, McGinnis MR. Fontana-Masson-stained tissue from culture-proven mycoses. *Arch Pathol Lab Med*. 1998;122:1107–1111.
79. Sharkey PK, Graybill JR, Rinaldi MG, et al. Itraconazole treatment of phaeohyphomycosis. *J Am Acad Dermatol*. 1990;23:577–586.
80. Whittle DI, Kominos S. Use of itraconazole for treating subcutaneous phaeohyphomycosis caused by *Exophiala jeanselmei*. *Clin Infect Dis*. 1995;21:1068.
81. Al-Abdely HM, Akkunaizi AM, Al-Tawfiq JA, et al. Successful therapy of cerebral phaeohyphomycosis due to *Ramichloridium mackenziei* with the new triazole posaconazole. *Med Mycol*. 2005;43:91–95.
82. Negroni R, Helou SH, Petri N, et al. Case study: posaconazole treatment of disseminated phaeohyphomycosis due to *Exophiala spinifera*. *Clin Infect Dis*. 2004;38:e15–e20.
83. Agger WA, Andes D, Burgess JW. *Exophiala jeanselmei* infection in a heart transplant recipient successfully treated with oral terbinafine. *Clin Infect Dis*. 2004;38:e112–e115.
84. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. *JAMA*. 2006;296:953–963.
85. Guilhermetti E, Takahachi G, Shinobu CS, et al. *Fusarium* spp. as agents of onychomycosis in immunocompetent hosts. *Int J Dermatol*. 2007;46:822–826.
86. Nucci M, Anaissie E. Cutaneous infection by *Fusarium* species in healthy and immunocompromised hosts: implications for diagnosis and management. *Clin Infect Dis*. 2002;35:909–920.
87. Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. *Clin Microbiol Rev*. 2007;20:695–704.
88. Wheeler MS, McGinnis MR, Schell WA, et al. *Fusarium* infection in burned patients. *Am J Clin Pathol*. 1981;75:304–311.
89. Testerman GM, Steagald MK, Colquitt LA, et al. Disseminated *Fusarium* infection in a multiple trauma patient. *South Med J*. 2008;101:320–323.
90. Strum AW, Grave W, Kwee WS. Disseminated *Fusarium oxysporum* infection in a patient with heat stroke. *Lancet*. 1989;1:968.
91. Boutati EI, Anaissie EJ. *Fusarium,* a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood*. 1997;90:999–1008.
92. Krcméry V, Jesenska Z, Spanik S, et al. Fungaemia due to *Fusarium* spp. in cancer patients. *J Hosp Infect*. 1997;36:223–228.
93. Martino P, Gastaldi R, Raccah R, et al. Clinical patterns of *Fusarium* infections in immunocompromised patients. *J Infect*. 1994;28:7–15.
94. Nucci M, Marr KA, Queiroz-Telles F, et al. *Fusarium* infection in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2004;38:1237–1242.
95. Ammari LK, Puck JM, McGowan KL. Catheter-related *Fusarium solani* fungemia and pulmonary infection in a patient with leukemia in remission. *Clin Infect Dis*. 1993;16:148–150.
96. Raad I, Hachem R. Treatment of central venous catheter-related fungemia due to *Fusarium oxysporum*. *Clin Infect Dis*. 1995;20:709–711.
97. Girmenia C, Arcese W, Micozzi A, et al. Onychomycosis as a possible origin of disseminated *Fusarium solani* infection in a patient with severe aplastic anemia. *Clin Infect Dis*. 1992;14:1167.
98. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic *Fusarium* species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. *Clin Infect Dis*. 2001;33:1871–1878.
99. Pires-Goncalves RH, Sartori FG, Montanari LB, et al. Occurrence of fungi in water used at a haemodialysis centre. *Lett Appl Microbiol*. 2008;46:542–547.
100. Krcméry V, Spanik S, Kunova A, et al. Breakthrough fungemia appearing during empiric therapy with amphotericin B. *Chemotherapy*. 1997;43:367–370.
101. Cudillo L, Girmenia C, Santilli S, et al. Breakthrough fusariosis in a patient with acute lymphoblastic leukemia receiving voriconazole prophylaxis. *Clin Infect Dis*. 2005;40:1212–1213.
102. Kim MS, Lee HM, Sung HS, et al. Breakthrough disseminated fusariosis in an immunocompromised patient on voriconazole therapy. *Int J Dermatol*. 2012;51:621–623.
103. Bose P, Parekh HD, Holter JL, et al. Disseminated fusariosis occurring in two patients despite posaconazole prophylaxis. *J Clin Microbiol*. 2011;49:1674.
104. Liu K, Howell DN, Perfect JR, et al. Morphologic criteria for the preliminary identification of *Fusarium, Paecilomyces,* and *Acremonium* species by histopathology. *Am J Clin Pathol*. 1998;109:45–54.
105. Nelson PE, Dignani MC, Anaissie EJ. Taxonomy, biology, and clinical aspects of *Fusarium* species. *Clin Microbiol Rev*. 1994;7:479–504.
106. van Diepeningen AD, Brankovics B, Iltes J, et al. Diagnosis of *Fusarium* infections: approaches to identification by the clinical mycology laboratory. *Curr Fungal Infect Rep*. 2015;9:135–143.
107. Tortorano AM, Esposto MC, Prigitano A, et al. Cross-reactivity of *Fusarium* spp. in the *Aspergillus galactomannan* enzyme-linked immunosorbent assay. *J Clin Microbiol*. 2012;50:1051–1053.
108. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with haematologic malignancies and *Fusarium* infection. *Cancer*. 2003;98:315–319.
109. Wolff MA, Ramphai R. Use of amphotericin B lipid complex for treatment of disseminated cutaneous *Fusarium* infection in a neutropenic patient. *Clin Infect Dis*. 1995;20:1568–1569.
110. Apostolidis J, Bouzani M, Platsouka E, et al. Resolution of fungemia due to *Fusarium* species in a patient with acute leukemia treated with caspofungin. *Clin Infect Dis*. 2003;36:1349–1350.
111. Neuburger S, Massenkeil G, Seibold M, et al. Successful salvage treatment of disseminated cutaneous fusariosis with liposomal amphotericin B and terbinafine after allogeneic stem cell transplantation. *Transpl Infect Dis*. 2008;10:290–293.
112. Paphitou NI, Ostrosky-Zeichner L, Paetznick VL, et al. In vitro activities of investigational triazoles against *Fusarium* species: effects of inoculum size and incubation time on broth microdilution susceptibility test results. *Antimicrob Agents Chemother*. 2002;46:3298–3300.
113. Alastruey-Izquierdo A, Cuenca-Estrella M, Monzon A, et al. Antifungal susceptibility profile of clinical *Fusarium* spp. isolates identified by molecular methods. *J Antimicrob Chemother*. 2008;61:805–809.
114. Cordoba S, Rodero L, Vivot W, et al. In vitro interactions of antifungal agents against clinical isolates of *Fusarium* spp. *Int J Antimicrob Agents*. 2008;31:171–174.
115. Clancy CJ, Nguyen MH. The combination of amphotericin B and azithromycin as a potential new therapeutic approach to fusariosis. *J Antimicrob Chemother*. 1998;41:127–130.
116. Ortoneda M, Capilla J, Pastor FJ, et al. Efficacy of liposomal amphotericin B in treatment of systemic murine fusariosis. *Antimicrob Agents Chemother*. 2002;46:2273–2275.
117. Lozano-Chiu M, Arikan S, Paetznick VL, et al. Treatment of murine fusariosis with SCH 56592. *Antimicrob Agents Chemother*. 1999;43:589–591.
118. Graybill JR, Najvar LK, Gonzalez GM, et al. Improving the mouse model for studying the efficacy of voriconazole. *J Antimicrob Chemother*. 2003;51:1373–1376.
119. Raad II, Hachem RY, Herbrecht R, et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. *Clin Infect Dis*. 2006;42:1398–1403.
120. Spielberger RT, Falleroni MJ, Coene AJ, et al. Concomitant amphotericin B therapy, granulocyte transfusions, and GM-CSF administration for disseminated infection with *Fusarium* in a granulocytopenic patient. *Clin Infect Dis*. 1993;16:528–530.
121. Pastor FJ, Guarro J. Clinical manifestations, treatment and outcome of *Paecilomyces lilacinus* infections. *Clin Microbiol Infect*. 2006;12:948–960.
122. Guarro J, Gams W, Pujol I, et al. *Acremonium* species: new emerging fungal opportunists—in vitro antifungal susceptibilities and review. *Clin Infect Dis*. 1997;25:1222–1229.
123. Chouaki T, Lavarde V, Lachaud L, et al. Invasive infections due to *Trichoderma* species: report of 2 cases, findings of in vitro susceptibility testing, and review of the literature. *Clin Infect Dis*. 2002;35:1360–1367.
124. Castelli MV, Alastruey-Izquierdo A, Cuesta I, et al. Susceptibility testing and molecular classification of *Paecilomyces* spp. *Antimicrob Agents Chemother*. 2008;52:2926–2928.
125. Kratzer C, Tobudic S, Schmoll M, et al. *In vitro* activity and synergism of amphotericin B, azoles, and cationic antimicrobials against the emerging pathogen *Trichoderma* spp. *J Antimicrob Chemother*. 2006;58:1058–1061.
126. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, et al. Head-to-head comparison of the activities of currently available antifungal agents against 3,378 Spanish clinical isolates of yeasts and filamentous fungi. *Antimicrob Agents Chemother*. 2006;50:917–921.
127. Drogari-Apiranthitou M, Mantopoulou F, Skiada A, et al. *In vitro* antifungal susceptibility of filamentous fungi causing rare infections: synergy testing of amphotericin B, posaconazole and anidulafungin in pairs. *J Antimicrob Chemother*. 2012;67:1937–1940.
128. Iwen PC, Schutte SD, Florescu DF, et al. Invasive *Scopulariopsis brevicaulis* infection in an immunocompromised patient and review of prior cases caused by *Scopulariopsis* and *Microascus* species. *Med Mycol*. 2012;50:561–569.
129. Colombo AL, Padovan ACB, Chaves GM. Current knowledge of *Trichosporon* spp. and trichosporonosis. *Clin Microbiol Rev*. 2011;24:682–700.
130. Gueho E, Improvisi L, de Hoog GS, et al. *Trichosporon* in humans, a practical account. *Mycoses*. 1994;37:3–10.
131. Sugita T, Nishikawa A, Shinoda T. Identification of *Trichosporon asahii* by PCR based on sequences of the internal transcribed spacer regions. *J Clin Microbiol*. 1998;36:2742–2744.
132. Sugita T, Nishikawa A, Shinoda T, et al. Taxonomic position of deep-seated, mucosa associated, and superficial isolates of *Trichosporon cutaneum* from trichosporonosis patients. *J Clin Microbiol*. 1995;33:1368–1370.
133. Itoh T, Hosokawa H, Kohdera U, et al. Disseminated infection with *Trichosporon asahii*. *Mycoses*. 1996;39:195–199.
134. Dabas Y, Xess I, Kale P. Molecular and antifungal susceptibility study of trichosporonemia and emergence of *Trichosporon mycotoxinivorans* as a bloodstream pathogen. *Med Mycol*. 2017;55:518–527.
135. Haupt HM, Merz WG, Beschorner WE, et al. Colonization and infection with *Trichosporon* species in the immunosuppressed host. *J Infect Dis*. 1983;147:199–203.
136. Hung CC, Chang SC, Chen YC, et al. *Trichosporon beigelii* fungemia in patients with acute leukemia: report of three cases. *J Formos Med Assoc*. 1995;94:127–131.
137. Hajjeh RA, Blumberg HM. Bloodstream infection due to *Trichosporon beigelii* in a burn patient: case report and review of therapy. *Clin Infect Dis*. 1995;20:913–916.
138. Mirza SH. Disseminated *Trichosporon beigelii* infection causing skin lesions in a renal transplant patient. *J Infect*. 1993;27:67–70.
139. Nahass GT, Rosenberg SP, Leonardi CL, et al. Disseminated infection with *Trichosporon beigelii*. *Arch Dermatol*. 1993;129:1020–1023.
140. Walsh TJ, Newman KR, Moody M, et al. Trichosporonosis in patients with neoplastic disease. *Medicine (Baltimore)*. 1986;65:268–279.
141. Yong L, Hartmann T, Tao Z, et al. Breakthrough trichosporonosis in patients receiving echinocandins: case report and literature review. *Chin Med J*. 2012;125:2632–2635.
142. Hazirolan G, Canton E, Sahin S, et al. Head-to-head comparison of inhibitory and fungicidal activities of fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole against clinical isolates of *Trichosporon asahii*. *Antimicrob Agents Chemother*. 2013;57:4841–4847.
143. Chitasombat MN, Kofteridis DP, Jiang Y, et al. Rare opportunistic non-*Candida*, non-*Cryptococcus*) yeast bloodstream infections in patients with cancer. *J Infect*. 2012;64:68–75.
144. Dankner WM, Spector SA, Fierer J, et al. *Malassezia* fungemia in neonates and adults: complication of hyperalimentation. *Rev Infect Dis*. 1987;9:743–753.
145. Barber GR, Brown AE, Kiehn TE, et al. Catheter-related *Malassezia furfur* fungemia in immunocompromised patients. *Am J Med*. 1993;95:365–370.
146. Brooks R, Brown L. Systemic infections with *Malassezia furfur* in an adult receiving long-term hyperalimentation therapy. *J Infect Dis*. 1987;156:410–411.
147. Boekhout T, Kamp M, Geuho E. Molecular typing of *Malassezia* species with PFGE and RAPD. *Mol Mycol*. 1998;36:365–372.
148. Chang HJ, Miller HL, Watkins N, et al. An epidemic of *Malassezia pachydermatis* in an intensive care nursery associated with colonization of health care workers' pet dogs. *N Engl J Med*. 1998;338:706–711.
149. Powell DA, Marcon MJ. Failure to eradicate *Malassezia furfur* broviac catheter infection with antifungal therapy. *Pediatr Infect Dis J*. 1987;6:579–588.
150. Gupta AK, Kohli Y, Li A, et al. In vitro susceptibility of the seven *Malassezia* species to ketoconazole, voriconazole, itraconazole and terbinafine. *Br J Dermatol*. 2000;142:758–765.

151. Marcon MJ, Durreil DE, Powell DA, et al. In vitro activity of systemic antifungal agents against *Malassezia furfur*. *Antimicrob Agents Chemother*. 1987;31:951–953.
152. Perez-Sanchez I, Anguita J, Martin-Rabadan P, et al. *Blastoschizomyces capitatus* infection in acute leukemia patients. *Leuk Lymphoma*. 2000;39:209–212.
153. Martino R, Salavert M, Parody R, et al. *Blastoschizomyces capitatus* infection in patients with leukemia: report of 26 cases. *Clin Infect Dis*. 2004;38:335–341.
154. García-Ruiz JC, López-Soria L, Olazábal I, et al. Invasive infections caused by *Saprochaeta capitata* in patients with haematological malignancies: report of five cases and review of antifungal therapy. *Rev Iberoam Micol*. 2013;30:248–255.
155. Mazzocato S, Marchionni R, Fothergill AW, et al. Epiedmiology and outcome of systemi infections due to *Sapochaeta capitata:* case report and review of the literature. *Infection*. 2015;43:211–215.
156. Sanz MA, Lopez FA, Martinez ML, et al. Disseminated *Blastoschizomyces capitatus* infection in acute myeloblastic leukemia. *Support Care Cancer*. 1996;4:291–293.
157. Serena C, Marine M, Marimon R, et al. Effect of antifungal treatment in a murine model of blastoschizomycosis. *Int J Antimicrob Agents*. 2007;29:79–83.
158. Desnos-Ollivier M, Blanc C, Garcia-Hermoso D, et al. Misidentification of *Saprochaeta clavata* as *Magnusiomyces capitatus* in clinical isolates: utility of internal transcribed spacer sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometery and importance of reliable databases. *J Clin Microbiol*. 2014;52:2196–2198.
159. Vaux S, Criscuolo A, Desnos-Ollivier M, et al. Multicenter outbreak of infections causes by *Saprochaeta clavata,* an unrecognized opportunistic fungal pathogen. *MBio*. 2014;5:2309–2314.
160. Hazen KC. New and emerging yeast pathogens. *Clin Microbiol Rev*. 1995;8:462–478.
161. Fernadez-Ruiz M, Guinea J, Puig-Asensio M, et al. Fungemia due to rare opportunistic yeasts: data from a population-based surveillance in Spain. *Med Mycol*. 2017;55:125–136.
162. da Matta VLR, Melhem MC, Colombo AL, et al. Antifungal drug susceptibility profile of *Pichia anomala* isolates from patients presenting with nosocomial fungemia. *Antimicrob Agents Chemother*. 2007;51:1573–1576.
163. Thuler LC, Faivichenco S, Velasco E, et al. Fungaemia caused by *Hansenula anomala*—an outbreak in a cancer hospital. *Mycoses*. 1997;40:193–196.
164. Zaas AK, Boyce M, Schell W, et al. Risk of fungemia due to *Rhodotorula* and antifungal susceptibility testing of rhodotorula isolates. *J Clin Microbiol*. 2003;41:5233–5235.
165. Nunes JM, Bizerra FC, Ferreira RC, et al. Molecular identification, antifungal susceptibility profile, and biofilm formation of clinical and environmental *Rhodotorula* species isolates. *Antimicrob Agents Chemother*. 2013;57:382–389.
166. Munoz P, Bouza E, Cuenca-Estrella M, et al. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. *Clin Infect Dis*. 2005;40:1625–1634.
167. DiSalvo AF, Fielding AM, Ajello L. Infection caused by *Penicillium marneffei:* description of first natural infection in man. *Am J Clin Pathol*. 1973;59:259–263.
168. Segretain G. *Penicillium marneffei* n. sp., agent d'une mycose du système réticulo-endothélial. *Mycopathol Mycol Appl*. 1959;11:327–353.
169. Vanittanakom N, Cooper CR, Fisher MC, et al. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev*. 2006;19:95–110.
170. Supparatpinyo K, Khamwan C, Baosoung V, et al. Disseminated *Penicillium marneffei* infections in Southeast Asia. *Lancet*. 1994;344:110–113.
171. Drouhet E. Penicilliosis due to *Penicillium marneffei*: a new emerging systemic mycosis in AIDS patients traveling or living in Southeast Asia: review of 44 cases reported in HIV infected patients during the last 5 years compared to 44 cases of non AIDS patients reported over 20 years. *J Mycol Med*. 1993;4:195–224.
172. Duong TA. Infection due to *Penicillium marneffei,* an emerging pathogen: review of 155 reported cases. *Clin Infect Dis*. 1996;23:125–130.
173. Hung C, Hsueh P, Chen M, et al. Invasive infection caused by *Penicillium marneffei:* an emerging pathogen in Taiwan. *Clin Infect Dis*. 1998;26:202–203.
174. Kwan EYW, Lau YL, Yuen KY, et al. *Penicillium marneffei* infection in a non-HIV infected child. *J Paediatr Child Health*. 1997;33:267–271.
175. Sirisanthana V, Sirisanthana T. *Penicillium marneffei* infection in children infected with human immunodeficiency virus. *Pediatr Infect Dis J*. 1993;12:1021–1025.
176. Ajello L, Padhye AA, Sukroongreung S, et al. Occurrence of *Penicillium marneffei* infections among wild bamboo rats in Thailand. *Mycopathologia*. 1995;131:1–8.
177. Cooper CR. From bamboo rats to humans: the odyssey of *Penicillium marneffei*. *ASM News*. 1998;64:390–396.
178. Chariyalertsak S, Vanittanakom P, Nelson KE, et al. *Rhizomys sumatrensis* and *Cannomys badius,* new natural animal hosts of *Penicillium marneffei*. *J Med Vet Mycol*. 1996;34:105–110.
179. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, et al. Case-control study of the risk factors for *Penicillium marneffei* infection in human immunodeficiency virus–infected patients in northern Thailand. *Clin Infect Dis*. 1997;24:1080–1086.
180. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, et al. Seasonal variation of disseminated *Penicillium marneffei* infections in northern Thailand: a clue to the reservoir? *J Infect Dis*. 1996;173:1490–1493.
181. Le T, Wolbers M, Chi NH, et al. Epidemiology, seasonality, and predictors of outcome of AIDS-associated *Penicillium marneffei* infection in Ho Chi Minh City, Viet Nam. *Clin Infect Dis*. 2011;52:945–952.
182. Wu TC, Chan JWM, Ng CK, et al. Clinical presentations and outcomes of *Penicillium marneffei* infections: a series from 1994 to 2004. *Hong Kong Med J*. 2008;14:103–109.
183. Ko CI, Hung CC, Chen MY, et al. Endoscopic diagnosis of intestinal penicilliosis marneffei: report of three cases and review of the literature. *Gastrointest Endosc*. 1999;50:111–114.
184. Wortmann PD. Infection with *Penicillium marneffei*. *Int J Dermatol*. 1996;35:393–399.
185. Cheng NC, Won WW, Fung CP, et al. Unusual pulmonary manifestations of disseminated *Penicillium marneffei* infection in three AIDS patients. *Med Mycol*. 1998;36:429–432.
186. Deng Z, Ribas JL, Gibson DW, et al. Infections caused by *Penicillium marneffei* in China and southeast Asia: review of eighteen published cases and report of four more Chinese cases. *Rev Infect Dis*. 1988;10:640–652.
187. Le T, Chi NH, Cuc NTK, et al. AIDS-associated *Penicillium marneffei* infection of the central nervous system. *Clin Infect Dis*. 2010;51:1458–1462.
188. Hilmarsdottir I, Coutellier A, Elbaz J, et al. A French case of laboratory-acquired disseminated *Penicillium marneffei* infection in a patient with AIDS. *Clin Infect Dis*. 1994;19:357–358.
189. Jones PD, See J. *Penicillium marneffei* infection in patients infected with human immunodeficiency virus: late presentation in an area of nonendemicity. *Clin Infect Dis*. 1992;15:744.
190. Supparatpinyo K, Sirisanthana T. Disseminated *Penicillium marneffei* infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. *Clin Infect Dis*. 1994;18:246–247.
191. Cooper CR, McGinnis MR. Pathology of *Penicillium marneffei:* an emerging acquired immunodeficiency syndrome-related pathogen. *Arch Pathol Lab Med*. 1997;121:798–804.
192. Chaiyaroj SC, Chawengkirttikul R, Sirisinha S, et al. Antigen detection assay for identification of *Penicillium marneffei* infection. *J Clin Microbiol*. 2003;41:432–434.
193. Desakorn V, Simpson AJH, Wuthiekanun V, et al. Development and evaluation of rapid urinary antigen detection tests for diagnosis of *Penicillium marneffei*. *J Clin Microbiol*. 2002;40:3179–3183.
194. Huang Y, Hung C, Liao C, et al. Detection of circulating galactomannan in serum samples for diagnosis of *Penicillium marneffei* infection and cryptococcosis among patients infected with human immunodeficiency virus. *J Clin Microbiol*. 2007;45:2858–2862.
195. Sirisanthana T, Supparatpinyo K, Perriens J, et al. Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virus–infected patients. *Clin Infect Dis*. 1998;26:1107–1110.
196. Le T, Kinh NV, Cuc NTK, et al. A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. *N Engl J Med*. 2017;376:2329–2340.
197. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic *Penicillium marneffei* infections in AIDS patients. *Am J Trop Med Hyg*. 2007;77:350–353.
198. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus–infected patients with disseminated *Penicillium marneffei* infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother*. 1993;37:2407–2411.
199. Supparatpinyo K, Perriens J, Nelson KE, et al. A controlled trial of itraconazole to prevent relapse of Penicillium marneffei infection in patients infected with the human immunodeficiency virus. *N Engl J Med*. 1998;339:1739–1743.
200. Chaiwarith R, Charoenyos N, Sirisanthana T, et al. Discontinuation of secondary prophylaxis against penicilliosis marneffei in AIDS patients after HAART. *AIDS*. 2007;21:365–379.
201. Sudjaritruk T, Sirisanthana T, Sirisanthana V. Immune reconstitution inflammatory syndrome from *Penicillium marneffei* in an HIV-infected child: a case report and review of literature. *BMC Infect Dis*. 2012;12:1–6.
202. Herr RA, Tarcha EJ, Taborda PR, et al. Phylogenetic analysis of *Lacazia loboi* places this previously uncharacterized pathogen with the dimorphic Onygenales. *J Clin Microbiol*. 2001;39:309–314.
203. Taborda PR, Taborda VA, McGinnis MR. *Lacazia loboi* gen. nov., comb, nov., the etiologic agent of lobomycosis. *J Clin Microbiol*. 1999;37:2031–2033.
204. Burns RA, Roy JS, Woods C, et al. Report of the first human case of lobomycosis in the United States. *J Clin Microbiol*. 2000;38:1283–1285.
205. Al-Daraji WI, Husain E, Robson A. Lobomycosis in African patients. *Br J Dermatol*. 2008;159:234–236.
206. Papadavid E, Dalamaga M, Kapniari I, et al. Lobomycosis: a case from Southeastern Europe and review of the literature. *J Dermatol Case Rep*. 2012;6:65–69.
207. Elsayed S, Kuhn SM, Barber D, et al. Human case of lobomycosis. *Emerg Infect Dis*. 2004;10:715–718.
208. Bustamante B, Seas C, Salomon M, et al. Lobomycosis successfully treated with posaconazole. *Am J Trop Med Hyg*. 2013;88:1207–1208.
209. Anstead GM, Sutton DA, Graybill JR. Adiaspiromycosis causing respiratory failure and a review of human infections due to *Emmonsia* and *Chrysosporium* spp. *J Clin Microbiol*. 2012;50:1346–1354.
210. Mendes MO, Moraes MAP, Renoiner EIM. Acute conjunctivitis with episcleritis and anterior uveitis linked to adiaspiromycosis and freshwater sponges, Amazon region, Brazil, 2005. *Emerg Infect Dis*. 2009;15:633–639.
211. Schwartz IS, Kenyon C, Feng P, et al. 50 years of *Emmonsia* disease in humans: the dramatic emergence of a cluster of novel fungal pathogens. *PLoS Pathog*. 2015;11:e1005198.
212. Dot JM, Debourogogne A, Champigneulle J, et al. Molecular diagnosis of disseminated adiaspiromycosis due to *Emmonsia crescens*. *J Clin Microbiol*. 2009;47:1269–1273.
213. Kenyon C, Bonorchis K, Corcoran C, et al. A dimorphic fungus causing disseminated infection in South Africa. *N Engl J Med*. 2013;369:1416–1424.
214. Heys I, Taljaard J, Orth H. An *Emmonsia* species causing disseminated infection in South Africa. *N Engl J Med*. 2014;370:283–284.
215. Schwartz IS, Govender NP, Corcoran C, et al. Clinical characteristics, diagnosis, management, and outcomes of disseminated emmonsiosis: a retrospective case series. *Clin Infect Dis*. 2015;61:1004–1012.
216. Dukik K, Munoz JF, Jiang Y, et al. Novel taxa of thermally dimorphic systemic pathogens in the Ajellomycetaceae (Onygenales). *Mycoses*. 2017;60:296–309.
217. Schwartz IS, Lerm B, Hoving JC, et al. *Emergomyces africanus* in soil, South Africa. *Emerg Infect Dis*. 2018;24:377–380.
218. Maphanga TG, Britz E, Zulu TG, et al. In vitro antifungal susceptibility of yeast and mold phases of isolates of dimorphic fungal pathogen *Emergomyces africanus* (formerly *Emmonsia* sp.) from HIV-infected South African patients. *J Clin Microbiol*. 2017;55:1812–1820.
219. Rofael M, Schwartz IS, Sigler L, et al. *Emmonsia helica* infection in HIV-infected man, California, USA. *Emerg Infect Dis*. 2018;24:166–168.
220. Wang P, Kenyon C, de Hoog S, et al. A novel dimorphic pathogen, *Emergomyces orientalis* (Onygenales), agent of disseminated infection. *Mycoses*. 2017;60:310–319.
221. Schwartz IS, Sanche S, Wiederhold NP, et al. *Emergomyces canadensis,* a dimorphic fungus causing fatal systemic human disease in North America. *Emerg Infect Dis*. 2018;24:758–761.
222. Rosario MI, Roman FL, Batista AM, et al. Pigeons and their droppings as reservoirs of *Candida* and other zoonotic yeasts. *Rev Iberoam Micol*. 2017;34:211–214.
223. Lass-Florl C, Mayr A. Human protothecosis. *Clin Microbiol Rev*. 2007;20:230–242.
224. Krcméry V Jr. Systemic chlorellosis, an emerging infection in humans caused by algae. *Int J Antimicrob Agents*. 2000;15:235–237.
225. Masuda M, Hirose N, Ishikawa T, et al. *Prototheca miyajii* sp. nov., isolated from a patient with systemic protothecosis. *Int J Syst Evol Microbiol*. 2016;66:1510–1520.
226. Kim ST, Suh KS, Chae YS, et al. Successful treatment with fluconazole of protothecosis at the site of an intralesional corticosteroid injection. *Br J Dermatol*. 1996;135:803–806.

227. Carey WP, Kaykova Y, Bandres JC, et al. Cutaneous protothecosis in a patient with AIDS and severe functional defect: successful therapy with amphotericin B. *Clin Infect Dis*. 1997;25:1265–1266.
228. Polk P, Sanders DY. Cutaneous protothecosis in association with the acquired immunodeficiency syndrome. *South Med J*. 1997;90:831–832.
229. Narita M, Muder RR, Cacciarelli TV, et al. Protothecosis after liver transplantation. *Liver Transpl*. 2008;14:1211–1215.
230. Ahn A, Choe Y, Chang J, et al. Chronic eosinophilic meningoencephalitis by *Prototheca wickerhamii* in an immunocompetent boy. *Pediatr Infect Dis J*. 2017;36:687–689.
231. Matsumoto Y, Shibata M, Adachi A, et al. Two cases of protothecosis in Nagoya, Japan. *Australas J Dermatol*. 1996;37:S42–S43.
232. Tang WY, Lo KK, Lam WY, et al. Cutaneous protothecosis: report of a case in Hong Kong. *Br J Dermatol*. 1995;133:479–482.
233. Okuyama Y, Hamaguchi T, Teramoto T, et al. A human case of protothecosis successfully treated with itraconazole. *Nippon Ishinkin Gakkai Zasshi*. 2001;42:143–147.
234. Yun CH, Jeong JH, Ryu HR, et al. Cutaneous protothecosis responds rapidly to voriconazole. *Int J Dermatol*. 2016;55:1373–1377.
235. Gaastra WM, Lipman LJA, de Cock AWAM, et al. *Phythium insidiosum:* an overview. *Vet Microbiol*. 2010;148:1–18.
236. Krajaejun T, Sathapatayavongs B, Pracharktam R, et al. Clinical and epidemiological analyses of human pythiosis in Thailand. *Clin Infect Dis*. 2006;43:569–576.
237. Lelievre L, Borderie V, Garcia-Hermoso D, et al. Case report: imported *Pythium insidiosum* keratitis after a swim in Thailand by a contact-wearing traveler. *Am J Trop Med Hyg*. 2015;92:270–273.
238. Franco DM, Aronson JF, Hawkins HK, et al. Systemic *Pythium insidiosum* in a pediatric burn patient. *Burns*. 2010;36:e68–e71.
239. Sudjaritruk T, Sirisanthana V. Successful treatment of a child with vascular pythiosis. *BMC Infect Dis*. 2011;11:33–36.
240. Calvano TP, Blatz PJ, Vento TJ, et al. *Pythium aphanidermatum* infection following combat trauma. *J Clin Microbiol*. 2011;49:3710–3713.
241. Evriviades D, Jeffery S, Cubison T, et al. Shaping the military wound: issues surrounding the reconstruction of injured servicemen at the Royal Centre for Defence Medicine. *Phil Trans R Soc B*. 2011;366:219–230.
242. Sermsathanasawadi N, Praditsuktavorn B, Hongku K, et al. Outcomes and factors influencing prognosis in patients with vascular pythiosis. *J Vasc Surg*. 2016;64:411–417.
243. Salipante SJ, Hoogestraat DR, SenGupta DJ, et al. Molecular diagnosis of subcutaneous *Pythium insidiosum* infection by use of PCR screening and DNA sequencing. *J Clin Microbiol*. 2012;50:1480–1483.
244. Permpalung N, Worasilchai N, Plongla R, et al. Treatment outcomes of surgery, antifungal therapy and immunotherapy in ocular and vascular human pythiosis: a retrospective study of 18 patients. *J Antimicrob Chemother*. 2015;70:1885–1892.
245. Jesus FPK, Ferreiro L, Loreta ES, et al. In vitro synergism observed with azithromycin, clarithromycin, minocycline, or tigecycline in association with antifungal agents against *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2014;58:5621–5625.
246. Loreto ES, Tondolo JSM, Pilotto MB, et al. New insights into the in vitro susceptibility of *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2014;58:7534–7537.
247. Mahl DL, de Jesus FPK, Loreto ES, et al. *In vitro* susceptibility of *Pythium insidiosum* isolates to aminoglycoside antibiotics and tigecycline. *Antimicrob Agents Chemother*. 2012;56:4021–4023.
248. Itaqui SR, Verdi CM, Tondolo JSM, et al. In vitro synergism between azithromycin or terbinafine and topical antimicrobial agents against *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2016;60:5023–5025.
249. Jesus FPK, Loreto ES, Ferreiro L, et al. In vitro and in vivo antimicrobial activities of minocycline in combination with azithromycin, clarithromycin, or tigecycline against *Pythium insidiosum*. *Antimicrob Agents Chemother*. 2016;60:87–91.
250. Fredricks DN, Jolley JA, Lepp PW, et al. *Rhinosporidium seeberi:* a human pathogen from a novel group of aquatic protistan parasites. *Emerg Infect Dis*. 2000;6:273–282.
251. Herr RA, Ajello L, Taylor JW, et al. Phylogenetic analysis of *Rhinosporidium seeberi*'s 18S small-subunit ribosomal DNA groups this pathogen among members of the protoctistan *Mesomycetozoa* clade. *J Clin Microbiol*. 1999;37:2750–2754.
252. Vilela R, Mendoza L. The taxonomy and phylogenetics of the human and animal pathogen *Rhinosporidium seeberi:* a critical review. *Rev Iberoam Micol*. 2012;29:185–199.
253. Sudarshan V, Goel NK, Gahine R, et al. Rhinosporidiosis in raipur, chhattisgarh: a report of 462 cases. *Indian J Pathol Microbiol*. 2007;50:718–721.
254. Dutta S, Haldar D, Dutta M, et al. Socio-demographic correlates of rhinosporidiosis: a hospital-based epidemiologic study in Purulia, India. *Indian J otolaryngol Head Neck Surg*. 2017;69:108–112.
255. Karthikeyan P, Vijayasundaram S, Pulimoottil DT. A retrospective epidemiological study of rhinosporidiosis in a rural tertiary care centre in Pondicherry. *J Clin Diagn Res*. 2016;10:MC4–MC8.
256. Lasser A, Smith HW. Rhinosporidiosis. *Arch Otolaryngol*. 1976;102:308–310.
257. Reidy JJ, Sudesh S, Klafter AB, et al. Infection of the conjunctiva by *Rhinosporidium seeberi*. *Surv Ophthalmol*. 1997;41:409–413.
258. Snidvongs ML, Supanakorn S, Supiyaphun P. Severe epistaxis from rhinosporidiosis: a case report. *J Med Assoc Thai*. 1998;81:555–558.
259. Thappa DM, Venkatesan S, Sirka CS, et al. Disseminated cutaneous rhinosporidiosis. *J Dermatol*. 1998;25:527–532.

269 *Pneumocystis* Species

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SHORT VIEW SUMMARY

Definition
- *Pneumocystis* spp. are genetically distinct, host-specific opportunistic fungal pathogens widely found in nature.
- *Pneumocystis jirovecii,* found in humans, causes pneumonia ("*Pneumocystis* pneumonia" or PCP") in immunocompromised patients.

Epidemiology
- Infection is acquired by inhalation of the cystic form (ascus) of the organism.
- Primary infection occurs in the first 2 years of life in most people.
- Person-to-person transmission and outbreaks of PCP in immunosuppressed patients have been reported.
- Environmental factors influence PCP hospitalizations.
- Colonization is common, associated with obstructive airway disease.

Diagnosis
- PCP in patients with human immunodeficiency virus (HIV): slow development, milder disease, 10% to 12% mortality
- PCP in non-HIV patients: rapid development, severe disease, 30% to 50% mortality
- Gold standard: microscopic demonstration of organism in respiratory tract specimens by immunofluorescence or special stains
- Other methods (polymerase chain reaction, β-1,3-D-glucan levels) are promising but considered investigational

Treatment
- Trimethoprim-sulfamethoxazole (TMP-SMX) 15 to 20 mg/kg/day (TMP) and 75 to 100 mg/kg/day (SMX) IV or PO in divided doses every 6 to 8 hours for 14 to 21 days is the treatment of choice for mild, moderate, or severe PCP.
- *Mild-to-moderate PCP*: Oral dose can be given as TMP-SMX two double-strength (DS) tablets orally three times a day.
- Several alternative regimens are available depending on the severity of PCP.
- Prednisone 40 mg PO twice daily on days 1 to 5, 40 mg PO every day on days 6 to 10, and 20 mg PO every day on days 11 to 21 are given as adjunctive therapy for moderate-to-severe PCP (PaO_2 ≤70 mm Hg, or alveolar-arterial O_2 gradient >35 mm Hg).
- Start prednisone as soon as possible or within the first 3 days after beginning antimicrobial therapy.
- Prednisone is mainly indicated for HIV-positive patients.

Prevention
- TMP-SMX one DS tablet orally every day or one single-strength tablet orally every day is the drug of choice for primary and secondary prophylaxis.
- Alternative regimens are available.
- Evidence does not support isolation of PCP patients from contact with other immunocompromised hosts.

Pneumocystis was discovered in 1909 in Brazil by Carlos Chagas, who mistakenly interpreted the organism as a trypanosome. In 1912 Pierre and Eugénie Delanöe, in Paris, identified *Pneumocystis* as a separate genus and species and named the organism in honor of Antonio Carini, another researcher. *Pneumocystis* first came to medical attention when in the 1940s–50s it was identified as the cause of interstitial plasma cell pneumonia in institutionalized and debilitated infants in central and eastern Europe. In the 1960s *Pneumocystis* became widely appreciated as an important cause of pneumonia (now termed *Pneumocystis* pneumonia, or PCP) in immunocompromised hosts; however, with the development of safe and effective antimicrobial drugs, interest in the organism waned. The dramatic rise in the incidence of PCP, associated with human immunodeficiency virus (HIV) infection in the 1980s, rekindled interest in *Pneumocystis* as a major medical and public health problem. During the 1990s advances in the treatment of HIV reduced the frequency of PCP and other complications. Nevertheless, *Pneumocystis* remains a leading cause of opportunistic infection, morbidity, and mortality in these patients.[1] It is estimated that there are more than 400,000 annual cases of PCP worldwide, with more than 52,000 deaths per year.[2] Interest in the organism has also been spurred by studies of *Pneumocystis* colonization and its association with infant sudden unexpected death,[3] chronic obstructive pulmonary disease (COPD), and asthma[4]; and also the observed increase in cases of PCP among the non–HIV-infected population; status post–organ transplantation; those with hematologic or rheumatologic conditions and in receipt of biologic disease-modifying agents[5]; continuing outbreaks of PCP in health care settings; and sequencing of the human *Pneumocystis* genome.[6,7]

[a]All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

PATHOGEN

Pneumocystis describes a genus of closely related unicellular fungi of low virulence found in the lungs of humans and a variety of mammals. The taxonomic status of the genus was resolved in the late 1980s, when analysis of the ribosomal RNA (rRNA) gene suggested that the organism is more closely related to fungi than to protozoa.[1] This conclusion has been confirmed at every molecular locus analyzed and by whole-genome sequence analysis. Phylogenetic studies place the organisms as ascomycetes on a deep basal branch among the archiascomycetes; however, *Pneumocystis* is unusual among fungi in that the organism lacks ergosterol in its plasma membranes and is insensitive to available antifungal drugs that target ergosterol biosynthesis.

Species within the genus demonstrate genotypic and phenotypic differences manifested by antigenic differences, ultrastructural morphologic differences, and host specificity.[1] Genetic studies have demonstrated differences between *Pneumocystis* spp. at a karyotypic level, in the organization and structure of gene families within specific genomes, and at a sequence level within individual genes. Whole-genome sequence analysis of *Pneumocystis carinii, Pneumocystis murina,* and *Pneumocystis jirovecii* confirm these differences and provide novel reagents to further characterize differences.[7,8] Structural genomic differences exist in the mitochondrial genomes in addition to those found in the nuclear genomes; the mitochondrial genome of *P. jirovecii* is circular, whereas those of *P. carinii* and *P. murina* are linear.[9,10] Not only are there genetic differences in *Pneumocystis* among different animal hosts, but there are also species or strain differences, or both, in organisms from the same host. Ultrastructural morphologic differences are evident only at the level of electron microscopy, whereas other phenotypic differences between species require specialized reagents to determine antigenic characterization or multilocus enzyme electrophoresis.

Experimental models have demonstrated that *Pneumocystis* taken from a given host species appears unable to proliferate in other host species. Associated with a better understanding of the host specificity and genetic differences among members of the genus *Pneumocystis,* a need has arisen to define individual species within the genus. In recognition that the organisms described by the Delanöes were isolated from infected rats, a formal taxonomic description of rat-derived species was made, retaining the name of *P. carinii.*[11,12] *Pneumocystis* isolated from humans was formally described as *P. jirovecii* in recognition of Otto Jirovec, whose group first identified *Pneumocystis* as a human pathogen and the causative agent of interstitial plasma cell pneumonia. A second species identified in rats has been named *Pneumocystis wakefieldiae,* whereas *P. murina* and *Pneumocystis oryctolagi* have been identified in mice and rabbits, respectively.[11]

Despite the strenuous efforts by many investigators, the lack of a reliable *Pneumocystis* in vitro cultivation system remains an intractable problem. Limited (up to 10-fold) replication of rat-derived organisms has been achieved in different cell lines and in axenic media.[13] A continuous culture system for rat- and human-derived *Pneumocystis* has been described but has proved difficult to reproduce and maintain. Short-term culture has been used to study *Pneumocystis* metabolism and susceptibility to antimicrobial drugs, but standardization and reproducibility among laboratories have not yet been achieved.

Studies of the life cycle of *Pneumocystis* have been based mainly on light and electron microscopic analysis of forms seen in infected lungs or in short-term culture (Fig. 269.1).[14] Three developmental stages of the organism are commonly seen in conjunction with additional intermediate forms. The trophic form is small (1–4 µm) and pleomorphic and commonly exists in clusters; this stage can be identified on Giemsa stain by its reddish nucleus and blue cytoplasm (Fig. 269.2A). In the asexual phase of the life cycle the trophic forms multiply by binary fission, although trophic binary fission is rarely visualized or documented. In the sexual phase the haploid trophic forms are postulated to conjugate to form a diploid zygote that becomes a 4- to 6-µm sporocyte (precyst); this form is difficult to distinguish from the other developmental stages at the light microscopic level. The sporocyte undergoes meiosis followed by mitosis, leading to the formation of the ascus (cyst), which contains eight haploid ascospores. The expression of meiosis-specific genes, such as the functionally conserved meiotic control kinase Ran1, the meiotic activator Mei2, and the meiosis-specific recombinase Dcm1, have been confirmed in the lungs of infected mammalian hosts, suggesting sexual replication occurs in the lungs of infected mammalian hosts.[15,16] The finding that the genomes of *P. jirovecii*, *P. murina,* and *P. carinii* all contain a single region with only three genes involved in mating-type differentiation supports the presence of a homothallic (self-fertile) sexual cycle.[8,17] The 5- to 8-µm ascus has a thick cell wall that stains well with stains such as methenamine silver or toluidine blue O (see Fig. 269.2B). The ascospores or intracystic bodies are formed by compartmentalization of nuclei and cytoplasmic organelles, exhibit different shapes, and appear to be released through a rent in the cell wall. Studies using echinocandin inhibitors of β-1,3-glucan (BG) synthase suggest that the cystic form is an integral part of the life cycle and critical for transmission.[18,19]

Biochemical and metabolic studies of *Pneumocystis* have been limited by the problems of culturing the organism.[19,20] Functional analyses of the *P. carinii* and *P. jirovecii* genomes are consistent with the lifestyles of obligate parasites with a reduced repertoire of amino-acid synthase genes and an abundance of transporter genes, suggesting limitations in the ability to synthesize essential nutrients and a necessity to scavenge these from their mammalian host.[7,21,22] The surface of *Pneumocystis* is rich in glucose and mannose, *N*-acetylglucosamine, and galactose

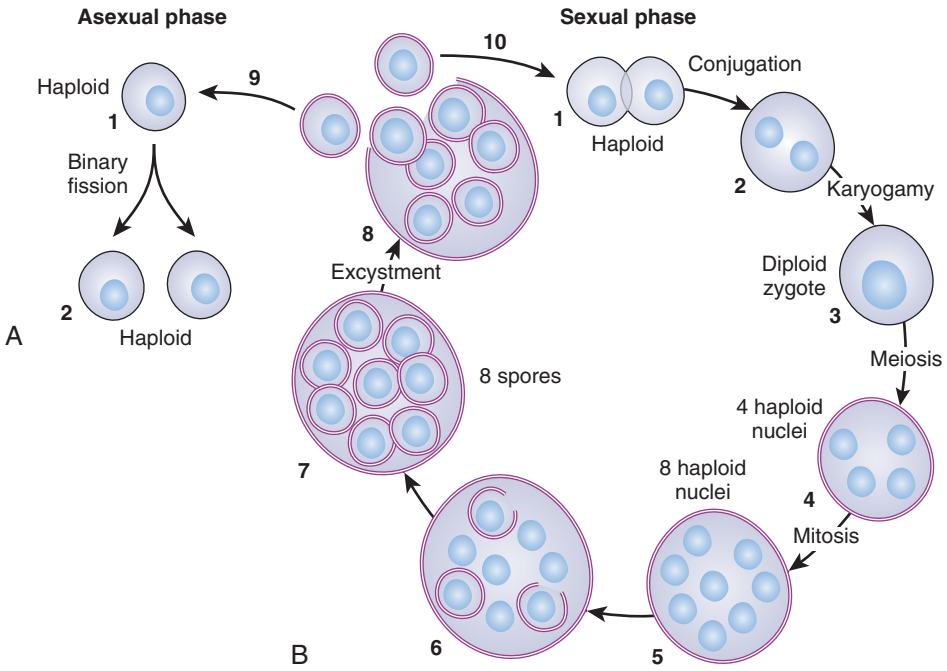

FIG. 269.1 Putative life cycle *of Pneumocystis*. The entry of *Pneumocystis* into the mammalian lung likely occurs during the first year of life. The agent of infection is suspected to be airborne spores. Recent studies suggest that the cyst/ascus (containing eight spores) may be the agent of infection. After inhalation, the spores ultimately take residence in the terminal portion of the respiratory tree, the alveoli. Neither the mechanism of migration to the alveoli nor the form in which the organism arrives in the alveoli (intact ascus or individual spores) is known. (A) Asexual phase: Haploid trophic forms are thought to replicate asexually by binary fission, whereby the nuclear content is duplicated *(1)* along with cellular contents that *(2)* divide into two haploid trophic forms. (B) Sexual phase: Two presumptive mating types conjugate *(1),* undergo karyogamy *(2),* and produce a diploid zygote *(3)* that progresses through meiosis to produce four haploid nuclei *(4),* followed by an additional mitosis to produce eight nuclei *(5).* The nuclei are packaged into spores by invagination of the ascus cell membranes *(6)* to produce eight double-membrane spores *(7).* After completion, excystment occurs via a protunicate release by unknown mechanisms *(8).* The released spores become the vegetative forms that can then undergo asexual *(9)* or sexual replication with a presumed opposite mating type *(10).* The mechanism of exit out of the lung and the life-cycle form that transits into the environment are unknown (the life cycle was composed using SmartDraw 10 (SmartDraw Software; San Diego). *(From Cushion MT. Are members of the fungal genus* Pneumocystis *(a) commensals; (b) opportunists; (c) pathogens; or (d) all of the above?* PLoS Pathog. *2010;6:e1001.)*

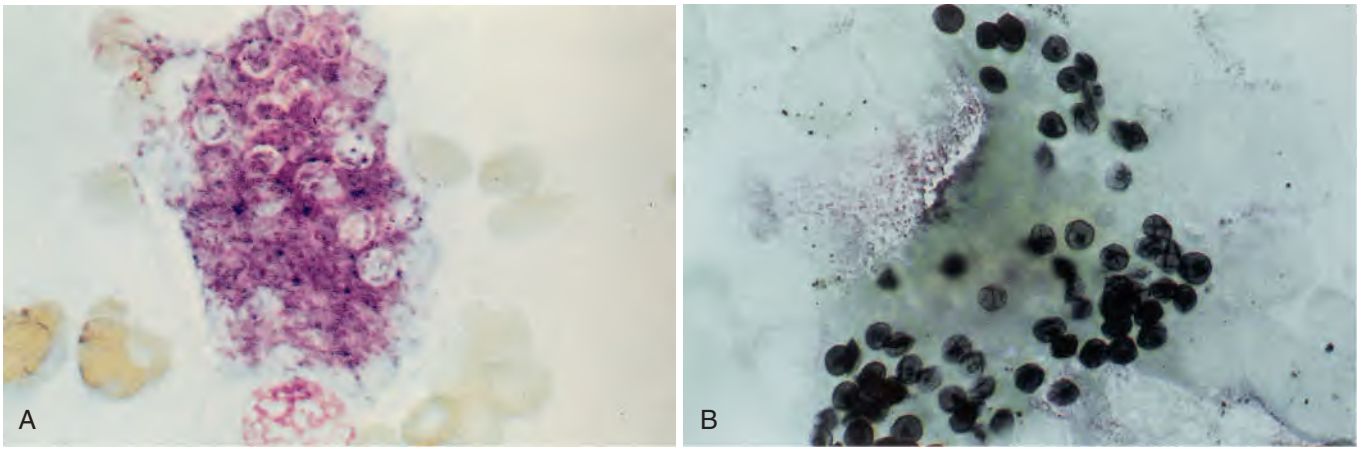

FIG. 269.2 Pneumocystis organisms. (A) Cluster of *Pneumocystis* trophic and cystic forms (Diff-Quik, ×1000). (B) Cluster of *Pneumocystis* cysts (Grocott-Gomori methenamine silver stain, ×1250).

N-acetylgalactosamine residues. The cell walls of cysts and trophic forms contain a number of immunogenic glycoproteins that may be part of a large complex (see Fig. 269.2).[23] BGs are a major component of the cell wall, whereas little or no chitin has been detected, although a chitin synthase has been detected, and upregulation of host chitinase activity is noted in the lung during infection.[24] Lipids have received considerable attention because of their relationship with antifungal therapy. Cholesterol is the dominant sterol present in *Pneumocystis*.[20] Instead of ergosterol, the organism synthesizes distinct Δ^7 C24 alkylated sterols. Coenzyme Q10 (CoQ10) is the major ubiquinone homologue synthesized by the organism; CoQ10 homologues, such as 8-aminoquinolones and hydroxynaphthoquinones, have shown good activity against the organism. A variety of enzymes and metabolic pathways have been characterized as potential therapeutic targets.[25,26]

Several major groups of *Pneumocystis* antigens have been identified. The 95- to 140-kilodalton (kDa) major surface glycoprotein (Msg), or gpA, is highly immunogenic, exhibits shared and species-specific antigenic determinants, and contains protective B- and T-cell epitopes.[27–31] Immunization with Msg also elicits a protective response in some, but not all, animal models.[31] Msg also facilitates interaction with host cells by adherence to the extracellular matrix proteins fibronectin, vitronectin, possibly laminin, the surfactant proteins A and D, and the mannose receptor.[32–37] Msg is composed of up to 10% N-linked carbohydrates, particularly mannose, which participate in the binding to these proteins.

Msg actually represents a complex family of proteins encoded by multiple genes that are arranged in clusters at the ends of chromosomes. Transcription of Msg genes occurs at a single expression site, termed the *upstream conserved sequence* (UCS), which is thought to result in only one Msg isoform being expressed on the surface of *Pneumocystis* at a time.[27–40] Changing the Msg gene at the UCS, by recombination and gene conversion, changes the surface Msg, resulting in antigenic variation. This ability to undergo antigenic variation may be an important mechanism whereby *Pneumocystis* evades the host immune response.[25] Studies suggest that antigenic variation and evasion of the host immune response may occur at both the cellular immune level and the humoral level.[38] Recombinant Msg preparations have overcome the previous limitations of crude *Pneumocystis* antigen preparations and offer promise to be helpful serologic tools. Variants of the recombinant Msg antigens have been used to better characterize the reactivity of the humoral responses in a number of studies.[41–44]

A second family of surface antigens was identified during studies characterizing Msg. A subtilisin-like serine protease encoded by the *PRT1* gene, also known as the Kex multigene family, was localized to the surface of rat-derived *Pneumocystis*.[45] In *P. murina* and *P. jirovecii* only a single key gene has been identified.[46] In other fungi these proteases are involved in the processing of preproteins as they make their way to the cell surface and may play a role in antigenic variation in *Pneumocystis.* There is a considerable body of evidence that Kex not only contains protective T-cell epitopes but also has protective B-cell epitopes. Immunization of $CD4^+$ cell–depleted mice with a Kex vaccine protects against the development of PCP and is protective in acquisition of *Pneumocystis* infection in immunosuppressed nonhuman primates.[6,47,48]

The third major antigen complex is a glycoprotein that migrates as a broad band of 45 to 55 and 35 to 45 kDa in rat and human *Pneumocystis,* respectively. The gene encoding a rat *Pneumocystis* 45- to 55-kDa antigen (p55) has been cloned and sequenced; the 3′ end of the molecule stimulates a host immune response.[49] Immunization with recombinant p55 antigen or DNA p55 encoding DNA afforded partial protection to subsequent infection.[50,51] Gene variation has also been demonstrated in the p55 gene, with up to five variants identified within the *Pneumocystis* genome.[52] The predicted amino-acid sequence of p55 shows a repeated motif rich in glutamic acid residues that, in other microbes, such as *Plasmodium,* has been suggested as a mechanism to divert the host immune response.[53] The 35- to 45-kDa band of human *Pneumocystis* is frequently found in respiratory tract specimens and is also recognized by serum antibodies.

EPIDEMIOLOGY

Pneumocystis infection is mainly acquired by inhalation, and recent evidence suggests that the infective form is the cystic form or ascus.[18] In addition, there are reports of *trans*-placental or vertical transmission.[52] Primary infection is acquired early in life, and infants probably serve as the natural host. This infection can either be asymptomatic or manifested by mild (usually upper) respiratory illness.[53,54] Serologic studies in different geographic locations have shown that most (≈80%) healthy children have been exposed to *Pneumocystis* by 2 to 3 years of age.[53,55] Cross-sectional studies by investigators in Chile, who used the polymerase chain reaction (PCR) amplification of the *P. jirovecii mtLSU* rRNA gene, found the prevalence of *P. jirovecii* colonization to be 52% in infants and 65% in adults who died and were autopsied in Santiago.[3,56]

Over the past decade there has been significant interest in *P. jirovecii* colonization. Risk factors for colonization include immunosuppressive conditions (HIV, low CD4 cell count, cancer, autoimmune diseases, organ transplantation); immunosuppressive drugs (corticosteroids, tumor necrosis factor-α [TNF-α] inhibitors); COPD and other chronic lung disorders; other conditions (pregnancy, cigarette smoking); treatment with ibrutinib or idelalisib; and lack of surfactant protein A in mice.[6,57,58] Colonization also varies in different geographic areas. The prevalence of colonization in healthy subjects is estimated to be about 20%.[6] The duration of colonization is variable. A study of a nonhuman primate colony revealed that all of the animals became colonized over a 2-year period, and the average duration of colonization was about 2 months.[59]

P. jirovecii colonization can have several consequences. Colonization is thought to precede the development of PCP but does not necessarily lead to PCP.[60] When PCP does develop, the *P. jirovecii* genotype associated

with pneumonia is often the same as in the genotype in colonization. Patients colonized with *P. jirovecii* can transmit the infection to others, and when recipients are immunosuppressed, PCP can result. Colonization is an independent risk factor for the development of airway obstruction, more severe PCP, or both; increased levels of matrix metalloprotease 12, an important contributor to the development of COPD; and an increased systemic inflammatory response.[6] Nonhuman primates infected with simian-human immunodeficiency virus (SHIV) that became colonized with *Pneumocystis* spontaneously developed progressive COPD, whereas SHIV-infected primates not colonized with *Pneumocystis* did not.[61]

PCP in HIV patients was first reported in 1981, and its incidence increased dramatically in high-income countries throughout the 1980s.[62] The number of cases were several orders of magnitude greater than in non-HIV patients. With widespread use of PCP chemoprophylaxis and combination antiretroviral therapy (ART), the incidence has steadily fallen since the early 1990s.[63] PCP now mainly occurs in individuals who are unaware that they are HIV positive, lack access to medical care, or who are noncompliant with medication.[64] Yet PCP still remains a leading opportunistic infection in HIV-positive patients in North America, Europe, and Australasia. PCP is increasingly recognized in low- and middle-income countries.[65,66]

Risk factors for PCP in HIV-positive patients include low absolute and percentage $CD4^+$ cell count, oral candidiasis, fevers, nonadherence with medication, polymorphism in the FcγIIIa receptor, and possibly *P. jirovecii* colonization.[6]

By contrast with HIV-positive patients, the incidence of PCP in non-HIV patients is rising.[5] The likely reasons for the increase of PCP in non-HIV patients include broader use of new and standard regimens of immunosuppressive drugs. New agents include immunomodulators, such as TNF-α inhibitors, and B-cell modifiers. Conditions requiring the use of these compounds are cancer (solid tumors, hematologic malignancies), organ transplantation, rheumatologic and connective tissue disorders, and inflammatory bowel disease.[6,67] Evidence to guide clinicians in prevention of PCP in non-HIV patients are available (Table 269.1).[68–70]

TABLE 269.1 Patients at Risk of Developing *Pneumocystis* Pneumonia, Unless Prophylaxis Is Given

	HIV/AIDS	SOLID-ORGAN TRANSPLANT	HEMATOLOGIC MALIGNANCY	CONNECTIVE TISSUE DISEASE
Risk factor for developing PCP	• CD4 count <200 cells/mm³ • CD4 <14% of total lymphocyte count • Prior episode of PCP • High plasma HIV load	• CD4 count <200 cells/mm³ • Use of: Corticosteroids Antilymphocyte therapy, (e.g., alemtuzumab, mycophenolate mofetil) Calcineurin inhibitors • CMV disease • Allograft rejection • Prolonged neutropenia • Exposure to patients with PCP	• CD4 count <200 cells/mm³ • Lymphopenia • Use of: Monoclonal antibodies (e.g., rituximab) Immunosuppression to prevent rejection of allogenic hemopoietic SCT Purine analogues or high-dose corticosteroids for autologous SCT Chemotherapy (including R-CHOP14, FCR, ABVD, gemcitabine, high-dose methotrexate) • ALL, *or* lymphoproliferative disorders (multiple myeloma, CML, NHL) • GVHD	• CD4 count <200 cells/mm³ • Lymphopenia • Use of: Anti-TNF inhibitors Azathioprine Corticosteroids (≥20 mg prednisolone OD (or equivalent) for ≥4 wk) Cyclophosphamide Methotrexate Rituximab
Prophylaxis given to patients	• CD4 count <200 cells/mm³ • CD4 <14% of lymphocyte count • CD4 200–250 cells/mm³, if regular (e.g., 3 monthly) CD4 monitoring is not possible	• All solid-organ transplants • Use of prednisolone ≥20 mg OD for ≥4 wk • Recurrent or chronic CMV disease • When immunosuppression is increased to prevent transplant rejection • Prolonged neutropenia	• ALL • Allogenic hemopoietic SCT • 20 mg prednisolone for ≥4 wk) • Use of: Alemtuzumab Fludarabine/cyclophosphamide/ rituximab Optional: • Radiotherapy and high-dose corticosteroids for primary brain tumor/metastases • Lymphoma treated with R-CHOP14 or BEACOPP • Use of: Nucleoside analogs (fludarabine, cladribine, mycophenolate mofetil)	• ANCA-positive vasculitis (especially granulomatosis with polyangiitis) • Use of: Corticosteroids with other agents, e.g., azathioprine, cyclophosphamide, methotrexate, when used to treat SLE, *or* inflammatory myopathy (dermatomyositis, polymyositis)
Duration of prophylaxis	• When CD4 increases from <200 cells/mm³ to >200 cells/mm³ for >3 mo (reintroduce if CD4 falls to <200 cells/mm³) • When CD4 is 100–200 cells/mm³, if HIV plasma RNA level is below limits of quantification for 3–6 mo	• All solid-organ transplants: for 6–12 mo posttransplant • Consider lifelong prophylaxis for: Lung/small bowel transplant • History of prior PCP • Chronic CMV disease	• ALL: From induction to end of maintenance • Allogenic hemopoietic SCT: ≥6 mo after engraftment (and for as long as immunosuppression is ongoing) • Alemtuzumab: >6 mo after completion of treatment • Fludarabine/cyclophosphamide/ rituximab: ≥6 mo after completion of treatment	
Prophylaxis regimen	First choice: TMP-SMX, 1 double-strength (DS) tablet OD *or* 1 single-strength (SS) tablet OD Alternatives: Dapsone *or* dapsone *plus* pyrimethamine *plus* leucovorin, Aerosolized pentamidine (via Respirgard II nebulizer) Atovaquone	First choice: TMP-SMX, 1 SS tablet OD *or* 1 DS tablet OD (or three times per week) Alternatives: Dapsone Aerosolized pentamidine Atovaquone Clindamycin *plus* primaquine	First choice: TMP-SMX, 1 SS tablet OD *or* 1 DS tablet OD (or three times/wk) Alternatives: Dapsone Aerosolized pentamidine	First choice: TMP-SMX, 1 DS tablet OD *or* 1 SS tablet OD Alternatives: Dapsone, or dapsone *plus* pyrimethamine *plus* leucovorin Aerosolized pentamidine Atovaquone

TABLE 269.1 Patients at Risk of Developing *Pneumocystis* Pneumonia, Unless Prophylaxis Is Given—cont'd

	HIV/AIDS	SOLID-ORGAN TRANSPLANT	HEMATOLOGIC MALIGNANCY	CONNECTIVE TISSUE DISEASE
Notes	• Prophylaxis indicated for all HIV-infected adults, including pregnant women and those on ART • Prophylaxis not needed if receiving sulfadiazine-pyrimethamine for treatment or suppression of toxoplasmosis • TMP-SMX DS tablet protects against toxoplasmosis and many respiratory infections • Atovaquone is as effective as aerosolized pentamidine (but is more expensive) • If seropositive for toxoplasmosis, and patient cannot tolerate TMP-SMX, dapsone *plus* pyrimethamine *plus* leucovorin, *or* atovaquone ± pyrimethamine *plus* leucovorin are alternatives • Insufficient data to recommend: Aerosolized pentamidine given by devices other than Respirgard II Intermittently administered IV pentamidine Oral clindamycin *plus* primaquine (could consider these regimens if recommended agents cannot be administered or are not tolerated)			

ABVD, Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; *ALL,* acute lymphoblastic leukemia; *ANCA,* antineutrophil cytoplasmic antibody; *ART,* antiretroviral therapy; *BEACOPP,* bleomycin, doxorubicin (adriamycin), etoposide, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisolone *CML,* chronic myeloid leukemia; *CMV,* cytomegalovirus; *FCR,* fludarabine, cyclophosphamide, rituximab; *GVHD,* graft-versus-host disease; *HIV,* human immunodeficiency virus; *IV,* intravenous; *NHL,* non-Hodgkin lymphoma; *OD,* every day; *PCP, Pneumocystis jirovecii* pneumonia; *R-CHOP14,* rituximab, cyclophosphamide, doxorubicin, vincristine (Oncovin), prednisolone (given every 14 days); *SCT,* stem cell transplant; *SLE,* systemic lupus erythematosus; *TMP-SMX,* trimethoprim-sulfamethoxazole; *TNF,* tumor necrosis factor.
Data from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed May 19, 2017; Martin SI, Fishman JA, AST Infectious Diseases Community of Practice.* Pneumocystis *pneumonia in solid organ transplantation.* Am J Transpl. *2013;13:272–279; Maertens J, Cesaro S, Maschmeyer G, et al; 5th European Conference on Infections in Leukaemia (ECIL-5); a joint venture of the European Group for Blood and Marrow Transplantation (EBMT); European Organisation for Research and Treatment of Cancer (EORTC); Immunocompromised Host Society (ICHS); European LeukemiaNet (ELN). ECIL guidelines for preventing* Pneumocystis jirovecii *pneumonia in patients with haematological malignancies and stem cell transplant recipients.* J Antimicrob Chemother. *2016;71:2397–2404; and Wolfe RM, Peacock JE.* Pneumocystis *pneumonia and the rheumatologist: which patients are at risk and how can PCP be prevented?* Curr Rheumatol Rep. *2017;19:35.*

There is an ongoing debate about the mechanisms by which PCP develops. The older theory is reactivation of latent infection. *Pneumocystis* infection is acquired in early childhood, becomes part of the host's resident microbial flora, and remains dormant for long periods of time. With a decline in the host's immune function, active replication of the organism occurs and results in PCP. The alternative view, which is held by most investigators, is that exposure to *Pneumocystis* is transient and that individuals are frequently exposed to disparate environmental sources of the organism throughout their lives. These theories have different implications when developing infection control procedures for PCP in health care facilities. If *P. jirovecii* is communicable, patients with PCP should not have direct contact with other immunocompromised hosts.[71]

Several studies have raised the possibility of environmental sources of *Pneumocystis*. *Pneumocystis* DNA has been detected in the air and in pond water.[72] Outdoor activities, such as gardening and hiking, have been shown to be independent risk factors for PCP.[73] Geographic clusters of PCP in HIV-positive patients have been found in the United States in San Francisco and Cincinnati and in the United Kingdom.[74,75] Cases of PCP were mainly found in the more affluent areas of the US cities where there was more green space. These clusters suggested the possibility of either exposure to a common environmental source of *Pneumocystis* or to a specific location where many at-risk individuals gathered and spread of *P. jirovecii* occurred.

Studies of environmental factors affecting the occurrence of PCP have mainly focused on climatologic factors. The most frequent association has been the occurrence of PCP during the warmer parts of the year.[72] Another report found a significant monthly and seasonal variation in the occurrence of specific *P. jirovecii* genotypes.[76] In addition to season, air-pollution factors are related to PCP; increased ambient sulfur dioxide is associated with risk of hospitalization with PCP, but its effects are modified by increased levels of carbon monoxide.[77]

There is considerable evidence that *Pneumocystis* is communicable. Experimental transmission of *Pneumocystis* infection has been shown by close contact or the airborne route in immunodeficient, immunosuppressed, and normal mice, rats, and other animals.[72] There have been outbreaks of PCP in immunodeficient rodent colonies, as well as *Pneumocystis* colonization and transmission of *Pneumocystis* infection in commercial rodent colonies under strict barrier conditions.[78,79]

Outbreaks of PCP in humans occurred in crowded orphanages during World War II and in immunosuppressed patients in the 1960s and 1970s.[72] PCP outbreaks in immunosuppressed patients over the past several decades have occurred mainly in renal transplant recipients. A systematic review that examined 16 outbreaks involving about 200 patients over the past 3 decades revealed common problems, such as frequent interpatient contact, a lack of chemoprophylaxis, and a lack of adherence to isolation procedures.[80] No environmental source or seasonal occurrence of PCP was found. There was considerable mortality, but it decreased over time. *Pneumocystis* genotyping showed that most outbreaks were caused by a single or dominant strain of *P. jirovecii,* and that there was person-to-person transmission. Recommendations included isolation of PCP patients and use of chemoprophylaxis. Subsequent publications have emphasized the importance of *P. jirovecii* colonization and the need for chemoprophylaxis of these patients, revised chemoprophylaxis guidelines, and the importance of PCP in other immunosuppressed patient populations.[72]

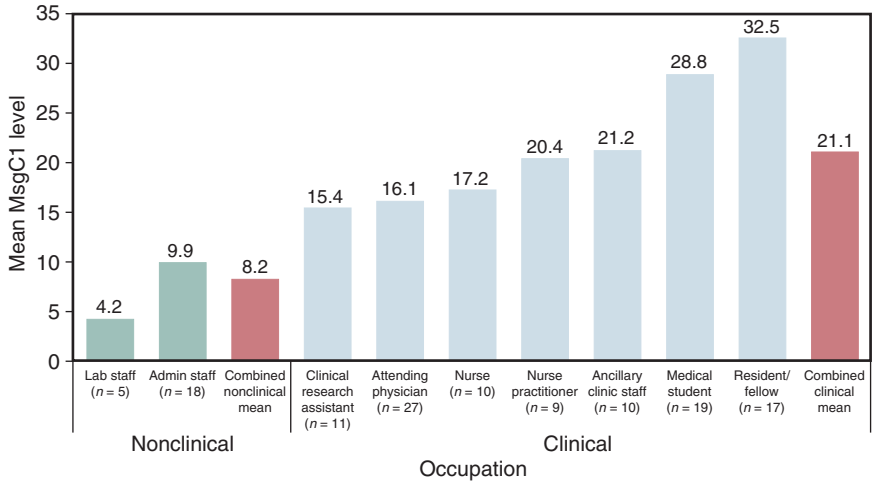

FIG. 269.3 Serologic study of San Francisco General Hospital health care workers. Major surface glycoprotein C1 (MsgC1) levels by occupation. Geometric mean MsgC1 antibody levels are shown for nonclinical and clinical staff, by job title. *(From Tipirneni R, Daly KR, Jarlsberg LG, et al. Healthcare worker occupation and immune response to* Pneumocystis jirovecii. Emerg Infect Dis. *2009;15:1590–1597.)*

Procedures to collect and quantify viable *Pneumocystis* organisms in the air of patients with PCP have been developed.[81] Viable *P. jirovecii* was detected in 80% of samples at 1 m from the bedside, in 33% of the samples at 8 m from the bedside, but not in the air at other locations inside or outside the hospital. These data support the idea that *P. jirovecii* infection can be spread from person-to-person by close contact and support the idea that patients with active PCP should be isolated from other immunocompromised (and thus at-risk) patients.

Serologic studies using crude antigen preparations have established that *P. jirovecii* infection is acquired early in life, so by age 2 or 3 years of age most (≈80%) children have been exposed to the organism[53,55]; however, these tests have lacked the sensitivity and specificity to be of help in other epidemiologic, clinical, or diagnostic studies.[51] The development of recombinant Msg fragments has helped investigators to overcome these problems. A sequential serologic study that followed up healthy infants during the first 2 years of life showed that the force or rate of infection was 8% to 10% per month, that a proportion of subjects developed recurrent episodes of *P. jirovecii* colonization, and that there were seasonal changes in these responses.[82] An analysis of health care workers showed that people who had clinical contact with patients have significantly higher antibody levels to *Pneumocystis* Msg fragments than workers who do not (Fig. 269.3).[43] This observation is important because it raises questions about whether health care workers might contribute to the spread of *P. jirovecii* in hospitals.

Other serologic studies have shown that *P. jirovecii* infection has worldwide distribution, but factors such as geography, smoking, and previous episodes of PCP independently affect antibody levels; that serology has promise as a method of diagnosing PCP; and that antibody levels to specific Msg fragments and recombinant Kex have prognostic value.[83–85]

PATHOLOGY AND PATHOGENESIS

After inhalation, the cystic stage of *Pneumocystis* releases the trophic forms, which initiate the infection by adhering to epithelial cells of the respiratory tract. Our current concepts of how this occurs are almost entirely based on studies of alveolar epithelial cells. The trophic form preferentially attaches to the alveolar type I cell, with close apposition of the cell surfaces but no fusion of the membranes.[86] Although the type I cell does not replicate, in vitro studies have shown that *Pneumocystis* attachment to cultured alveolar type II cells increased differentiation into a type I cell–like phenotype.[87] Other studies have shown that the adherence of *Pneumocystis* also occurs via extracellular matrix glycoproteins, resulting in altered gene expression, morphologic changes, and organism proliferation.

The attachment for *Pneumocystis* to lung epithelial cells requires an intact cytoskeleton and results in changes in both the organism and host.[88] *Pneumocystis* maintains an extracellular existence within alveoli and probably obtains essential nutrients from the alveolar fluid or living cells. This is supported by the finding of overexpression of multiple transporters found in the *Pneumocystis* genome and the corresponding absence of important synthetic genes.[89] In HIV-positive patients *Pneumocystis* also enhances HIV proliferation.[90] Another effect of the attachment is to suppress the growth of lung epithelial cells through cyclin-dependent kinase regulatory pathways.[91] Other reports have shown that the organism alters lung guanosine triphosphate–binding regulatory proteins and induces expression of intracellular adhesion molecule 1 and fibrinogen.[92] These properties may influence both the lung damage and host inflammatory and reparative responses in PCP.

Host defenses against *Pneumocystis* include innate immunity and adaptive or acquired immunity.[93] The innate immune system, which is the first level of defense, is composed of alveolar macrophages, surfactant protein (SP)-A, SP-D, and other factors. Because alveolar macrophages have early and late actions in the infection, they are discussed later in this chapter. SP-A is a pulmonary collectin that functions in host defense (e.g., as a nonimmune opsonin) and as an immune modulator. Immunosuppressed SP-A knockout mice develop higher infection levels of *Pneumocystis* and an increased host inflammatory response compared with wild-type mice.[94] The role of SP-D in host defenses is less clear, but it appears to modulate the inflammatory response in conditions such as the immune reconstitution inflammatory syndrome (IRIS).[95]

There is accumulating evidence that B cells and humoral immunity play an important part in host defenses against *Pneumocystis* infection. Natural immunoglobulin M (IgM) antibodies that recognize common fungal carbohydrate antigens have been discovered and may provide protection against early *Pneumocystis* infection.[96] PCP has been reported in patients and mice with B-cell defects or given medication (e.g., rituximab) that acts on B cells.[51,97] Mice depleted of CD4 T-cells after recovery from a primary infection are still protected from a secondary fungal challenge.[98,99] Depletion of CD8 T-cells or macrophages, which can mediate opsonic phagocytosis, abrogated protection in a secondary challenge model.[100] Studies in SHIV-positive primates have shown a correlation of acquired antibody levels to Kexin and susceptibility or resistance to *Pneumocystis* colonization.[101] A positive therapeutic effect has been found with the passive administration of hyperimmune serum or monoclonal antibodies to Msg and other antigens in experimental models of PCP.[29,30,101] Immunization with live *Pneumocystis* or Kex DNA with dendritic cells engineered to express CD40L, as a genetic adjuvant, protected CD4 cell–depleted mice from organism challenge and appeared to be mediated by antibodies via helper T cell (Th)1- or Th2-type responses.[102–104] A subsequent report showed that interleukin (IL)-23 produced by these dendritic cells played a critical role in eliciting recall antibody responses and that IL-23 might be of value as a potential

adjuvant.[105] Conserved antigens, such as the recently described PCA1 that is homologous between murine and human *Pneumocystis* spp., may serve as better vaccine targets.[106] B cells function as not only the source of antibodies but also as antigen-presenting cells and in helping the development of memory CD4 cells.[107] Antibodies contribute to host defenses against *Pneumocystis* by acting as opsonins.[51]

Analysis of the role of antibodies in humans has been difficult because of the high prevalence of serum antibodies in the population and the lack of information about which antigen epitopes are protective. HIV induces abnormalities in B-cell number and function, which results in impaired antibody responses to vaccines or microbial antigens.[108] In a South African cohort of children hospitalized with PCP, humoral responded to Msg antigens compared with HIV-uninfected PCP cases.[109] Recombinant Msg antigen fragments have shown promise in seroepidemiologic studies. Recent reports have suggested that low antibody levels in HIV patients to Kex are a risk factor for developing PCP,[85] and antibody levels to Msg are predictors of survival in hospitalized patients.[84] Although local bronchoalveolar lavage fluid (BALF) antibodies have received only limited attention, there is evidence of decreased antibody responses in HIV patients and in SHIV-positive nonhuman primates.[101,110–112]

Impaired cellular immunity has long been considered an important predisposing factor in the development of PCP.[51,86] Naturally occurring outbreaks of PCP have occurred in immunodeficient animals, particularly colonies of severe combined immunodeficiency disease (SCID) mice and athymic nude mice and rats.[78,113] The central role of $CD4^+$ cells in host defenses against this organism has been shown by cell depletion and reconstitution experiments and by knockout mice.[114–116] Other contributors to these defenses include T-cell costimulatory molecules, such as CD28 and CD2; the CD40 to CD40L pathway, which facilitates the interaction of T cells with B cells; and CD8 cells, which function as cytotoxic cells or by secreting cytokines.[115,117–122] The role of γδ T cells in host defenses against *Pneumocystis* is unclear, but it is thought that these cells might help recruit CD8 cells and modulate their effects.[6] Natural cells also play a role in host defenses against *Pneumocystis* but require $CD4^+$ cells to become activated.[105]

PCP can be induced in normal rodents by the administration of corticosteroids, and these models have been used for more than 3 decades.[86] Protein malnutrition and an immature immune system also impair host defenses against *Pneumocystis,* although the defect in neonatal mice is related more to factors in the lung milieu than to T cells.[123,124] The clearest evidence of the role of defective cell-mediated immunity in the development of PCP in humans comes from persons infected with HIV (see Table 269.1). The risk of developing PCP in adult HIV patients increases greatly when circulating CD4 cells fall below 200 cells/mm^3.[125] Because CD4 counts are much higher in young children than in adults, different criteria must be used. The presence of other clinical complications of HIV (e.g., fever and oral candidiasis) increases the risk of PCP independent of the CD4 count. Cases of PCP associated with CD4 counts <200 cells/mm^3 have been encountered in cancer patients receiving cytotoxic drugs, in adults with idiopathic CD4 lymphopenia, and in otherwise healthy individuals with subtle T-cell defects[126,127] (see Table 269.1).[128,129] In general, non-HIV patients have higher peripheral blood and BALF CD4 cells than HIV patients; however this patient group is often receiving corticosteroids and other immunosuppressive drugs that can lower $CD4^+$ cell counts.[130] There are clear guidelines based on $CD4^+$ counts and other risk factors for initiating PCP chemoprophylaxis in non-HIV patients.[131]

The occurrence of PCP in other patient populations with impaired cellular immunity include premature debilitated infants and children with primary immunodeficiency diseases, particularly SCID, which involves both T- and B-cell defects, and the hyper-IgM syndrome, which involves disruption of the CD40-CD40L pathway,[128] and patients receiving immunosuppressive drugs for the treatment of a variety of conditions (see Table 269.1).[132] The principal immunocompromised hosts at risk for PCP include patients with hematologic malignancies and solid tumors (e.g., brain tumors), solid-organ and bone marrow transplant recipients, and collagen vascular disorders such as granulomatosis with polyangiitis.[6,86,126,133–137] The number of these individuals has grown over the years with better survival and the more widespread use of cytotoxic and immunosuppressive therapies. Corticosteroids, used alone or in combination with other agents, such as infliximab, etanercept, and calcineurin inhibitors, remain the most common immunosuppressive drugs implicated in the development of PCP. The relationship of corticosteroids to *Pneumocystis* has been emphasized by the occurrence of PCP in patients with Cushing syndrome but also in children receiving corticosteroids for diseases such as asthma, which are not known to predispose to opportunistic infections.[138,139] Cases of PCP in patients on chemotherapy regimens without corticosteroids are described.[97] Protein malnutrition is an important risk factor for the development of PCP, both by itself and as a complication of the patient's underlying disease or chemotherapy. Lung factors (e.g., radiotherapy and fibrosis) have been suggested as additional predisposing factors in non-HIV patients.[86]

Alveolar macrophages are the first line of defense against *Pneumocystis* and the principal effector cell in clearing the organism from the lung.[140] Rodents depleted of macrophages are susceptible to *Pneumocystis* infection; however, activated macrophages in the absence of CD4 cells are unable to control *P. jirovecii* infection.[140,141] Recognition and adherence of *Pneumocystis* to macrophages occur by multiple pathways involving Msg and BG in the organism; extracellular matrix and surfactant proteins; and mannose, dectin-1, and Fc receptors.[32–37,142] Toll-like receptor 2 (TLR2) and TLR4 help regulate host cytokine responses.[143,144] Macrophages ingest, degrade, and kill *Pneumocystis,* releasing cytokines, such as TNF-α, eicosanoids, nitric acid, and reactive oxidants.[32–36,145–147] Macrophages also undergo apoptosis, which is mediated by polyamines.[148]

Both the life cycle form of *Pneumocystis* organisms and the type of macrophage response seems critical in organism clearance. The cystic form, which is rich in BG, is recognized by alveolar macrophages, dendritic cells, and lung epithelial cells and primes a robust T-cell–mediated response. Trophic forms lacking BG elicit reduced CD4 T-cell recruitment and interferon (IFN)-γ production. In addition, the trophic forms actively suppress the proinflammatory response initiated by cystic forms, in that trophic form–loaded dendritic cells had reduced capacity to stimulate CD4 T-cell proliferation and polarization, potentially promoting trophic form survival.[149] Recent studies demonstrated that classic macrophages (M1) predominate in the innate response to *Pneumocystis* infection in the absence of an intact immune system, such as seen in the immunosuppressed rat model, and were defective in clearing *P. carinii.* Immunocompetent animals had more prominent alternative macrophage (M2) responses with clearance of infection. Treatment of immunosuppressed rats with M2 cells reverted the animals to a protected phenotype.[150,151] Compared with alveolar macrophages from adult mice, macrophages from newborn mice are intrinsically unresponsive to *Pneumocystis* infection.[152] On the other hand, *Pneumocystis* infection of adult mice downregulates the transcription factor PU.1, which leads to decreased expression of dectin-1.[153] Recently, an intracellular isoform of osteopontin, a protein expressed by many cells, has been shown to play an important role in innate immunity in *Pneumocystis* infection.[154]

Alveolar macrophage function is impaired in HIV-positive patients and other immunosuppressed populations. HIV downregulates mannose receptor expression, which results in decreased binding and uptake of *Pneumocystis;* impairs MD88-associated TLR4 signaling; and changes the macrophage cytokine response.[155–157] *Pneumocystis* itself impairs phagocytosis by promoting shedding of the mannose receptor and enhances the replication of HIV.[90,158]

The BG in *Pneumocystis* cysts elicits inflammatory responses in macrophages and other types of lung cells that contribute to the lung damage in PCP. Alveolar epithelial cells secrete neutrophil chemoattractant proteins, TNF-α, IL-8 in humans and MIP-2 in rats, and other inflammatory mediators.[146,159] The process involves signal transduction and lactosylceramide, a prominent constituent of the alveolar epithelial cell microdomains.[159,160] BG also stimulates dendritic cells, which are antigen-presenting cells, to secrete IL-23 and IL-6; these latter cytokines then stimulate Th17 phenotype.[161]

Exposure to *Pneumocystis* or its antigens stimulates production of a multitude of cytokines and chemokines. Two proinflammatory cytokines, TNF-α and IL-1, have been shown to be important in host defenses against the organism, particularly in the early stages of the infections.[162,163] TNF helps recruit lymphocytes and monocytes, which

contribute to *Pneumocystis* clearance, and chemokines (e.g., IL-8) from alveolar epithelial cells as part of the inflammatory response. IL-6, another proinflammatory cytokine, has been produced in response to *Pneumocystis,* but its contributions to host resistance to the organism are unclear.[164] IFN-γ and granulocyte-macrophage colony-stimulating factor are important contributors to host defense by macrophage activation or in cooperation with TNF-α.[165,166] The role of IFN-γ is particularly complex, and the results obtained can vary, depending on the experimental design. Recent studies have shown that IL-12 and IL-23 also contribute to host defenses to *Pneumocystis*.[167,168] IL-10 has also been shown to modulate the host inflammatory response, but no role in the host defense against *Pneumocystis* has been found for IL-4 or granulocyte-colony stimulating factor.[169,170]

The pathologic changes that occur during the development of PCP in animal models and in humans are similar.[86] As the host defenses become compromised, *Pneumocystis* organisms begin to proliferate and gradually fill alveolar lumens. In the corticosteroid-treated rat model, the organism number increases from 10^5 per lung, or fewer, to 10^9 to 10^{10} per lung after 8 to 10 weeks of corticosteroid administration. The principal histologic finding is the formation of a foamy, eosinophilic alveolar exudate (Fig. 269.4); as the PCP increases in severity, there may also be hyaline membrane formation, along with interstitial fibrosis and edema. The host inflammatory response is usually inconspicuous and is characterized by type II cell proliferation (a typical reparative response) and scanty mononuclear cell infiltrate. SCID mice exhibit cytokine production only late in the course of PCP, when elevated levels of TNF-α and IL-1 are found in the lungs.[171] Several studies have shown that rats with corticosteroid-induced PCP, as well as HIV and non-HIV patients with the disease, have elevated levels of proinflammatory cytokines in their respiratory tract but not in the peripheral blood.[172–174] Some patients exhibit atypical findings, such as lack of the alveolar exudate or the development of cavitary lesions, granulomas, or microcalcifications.[175] On electron microscopy, there is increased alveolar-capillary permeability, followed by evidence of damage to the type I cell.[86] Physiologic changes include hypoxemia with an increased alveolar-arterial oxygen (PAO_2-PaO_2) gradient and respiratory alkalosis; impaired diffusing capacity, suggesting alveolar-capillary block; and alterations in lung compliance, total lung capacity, and vital capacity.[176,177] The resulting picture suggests diffuse lung damage similar to that seen in the acute respiratory distress syndrome.

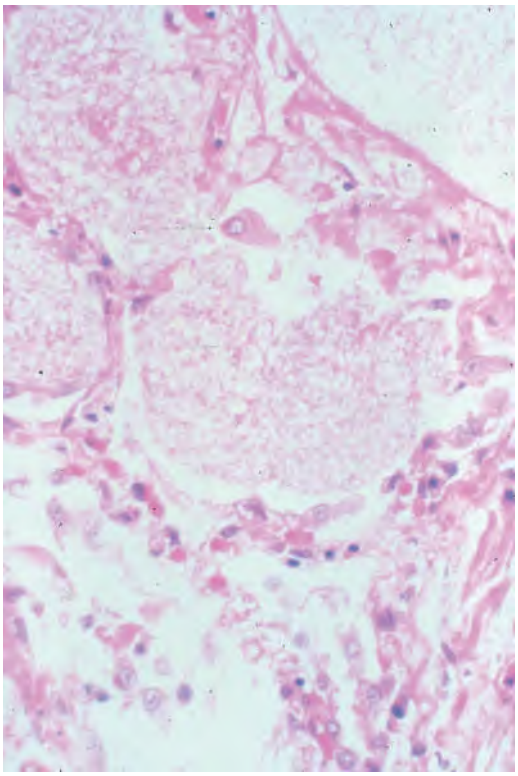

FIG. 269.4 Histologic findings in pneumocystosis. *Pneumocystis* pneumonia illustrating frothy eosinophilic honeycombed material filling the alveolar space (hemotoxylin and eosin stain, ×400).

The pathophysiologic changes described are caused not only by the effects of *Pneumocystis* on the type I cell but also alterations in the surfactant system and host inflammatory response. There is a fall in surfactant phospholipids (mainly phosphatidylcholine) that is caused by inhibition of phospholipid secretion mediated by Msg and other organism constituents.[178–181] Changes in the surfactant proteins include a decline in SP-B and SP-C and rise in SP-A and SP-D levels.[182,183] Fractionation of the surfactant has shown that most of the increased SP-A and SP-D levels are localized mainly in the small aggregate compartment.[184] There is now clear evidence that the host's immune inflammatory response to *Pneumocystis* can have harmful and helpful effects on the host lung. These effects are complex and depend to some degree on the experimental model being used. Immune reconstitution and cell depletion studies using SCID mice have shown that the clearance of PCP is associated with a hyperinflammatory response composed of increased proinflammatory cytokines and chemokines and reduced oxygenation and compliance.[185–188] These effects involve not only the complex interaction of CD4 cells and CD8 cells but also subsets of CD4 cells ($CD25^+$, $CD25^-$) and CD8 cells (TCI, TC2), which have effector or immune-modulatory functions.[189–194] In contrast to humans, neutrophils are a marker of inflammation and lung damage in mice but do not cause lung damage.[195] The administration of a large number of splenocytes or CD4 cells sensitized to Msg in rats with corticosteroid-induced PCP results in clinical illness and a cytokine cascade, along with a reduction in organism burden.[196] The presence of steroids has no apparent effect on these events. The contribution of the host inflammatory response to lung damage in HIV patients with PCP has been suggested by studies that have correlated increased numbers of neutrophils and levels of IL-8 in BALF with more severe pneumonia and worse prognosis.[197,198] IL-8 functions as a potent chemoattractant, its interaction with *P. jirovecii* is mediated by Msg, and its interaction with alveolar macrophages requires the coexpression of the mannose receptor and TLR2.[199–201] Alterations in eicosanoids, TNF-α, IL-1, other cytokines, and inflammatory mediators have also been noted in these and other studies; however, the pathogenic significance of these changes is unclear. HIV patients with PCP also frequently experience a worsening of respiratory function soon after receiving antimicrobial drugs. Corticosteroids, if given promptly, can ameliorate or prevent this outcome and improve survival.[202] It is thought that the beneficial effects of corticosteroids are attributable to their antiinflammatory properties or their effects on surfactant components; however, studies examining these issues have produced inconsistent results.[203–206]

CLINICAL MANIFESTATIONS

The presenting symptoms of PCP in the immunocompromised host are nonspecific and are mimicked by a wide variety of infectious and noninfectious etiologies. Presentation is typically with progressive exertional dyspnea, fever, and a nonproductive cough,[63,207] which is often associated with an inability to make a maximal inspiration (not due to chest pain).

On occasion, sputum is produced; hemoptysis is not a feature. Patients receiving immunosuppressive drugs frequently develop these clinical manifestations after the corticosteroid/immunosuppressive therapy agent dose has been tapered and are typically increasingly symptomatic for about 1 to 2 weeks before seeking medical attention. Among HIV-infected persons, symptoms are usually of longer duration than among medically immunosuppressed patients. HIV-infected patients frequently have prolonged prodromal periods with subtle clinical manifestations developing over 3 to 8 weeks; however, some individuals present with a fulminant worsening of symptoms over 7 to 10 days, or less; the intrapulmonary organism burden is higher, but lung damage is less severe.[208,209] Studies have also compared the clinical features of PCP in adult HIV patients by age and underlying risk group.[210,211] In both HIV-infected and non–HIV-infected patients, however, the clinical picture is variable; for

example, lung allograft recipients who develop PCP are frequently asymptomatic at the time of diagnosis.

On physical examination, varying degrees of respiratory distress may be evident (manifest as tachycardia, central cyanosis, use of accessory muscles of respiration), as well as stigmata of immunodeficiency/treatment-induced immune suppression (e.g., after receipt of chemotherapy or immunosuppressive medication posttransplantation), including molluscum contagiosum, seborrheic dermatitis, cutaneous Kaposi sarcoma, oral *Candida,* and oral hairy leukoplakia. Children may additionally demonstrate central cyanosis, flaring of the nasal alae, and intercostal retractions. Auscultation of the chest is usually normal; fine end-inspiratory crackles may be heard in about one-third of adults.[216]

Other Clinical Manifestations

The spread of *P. jirovecii* beyond the lungs is rarely encountered and occurs mainly in patients with advanced HIV infection who are taking no prophylaxis or only aerosolized pentamidine. The actual incidence of extrapulmonary pneumocystosis is unclear as the diagnosis is made by histologic examination of sites where there are clinical manifestations (e.g., lymph nodes, spleen, liver, bone marrow, gastrointestinal [GI] tract, eyes, thyroid, adrenal glands, and kidneys), or at autopsy.[212] Manifestations of extrapulmonary pneumocystosis include thyroid mass, pancytopenia from bone marrow necrosis, retinal cotton wool spots, and multiple hypodense splenic lesions on ultrasound or computed tomography (CT) scan. Biopsy or fine-needle aspiration shows areas of necrosis filled with foamy material. Grocott-Gomori methenamine silver (GMS) or fluorescent monoclonal antibody stain reveals numerous organisms.

Another clinical problem is the immune reconstitution inflammatory syndrome (IRIS) that occurs in HIV-infected patients days to months after starting ART, as the patient's immune system begins to recover with a rise in $CD4^+$ cells and is manifested as worsening of a known condition or a new condition.[213–215] IRIS occurs in up to 25% of HIV patients starting ART. The inciting agent can be a viable subclinical pathogen or a residual antigen from a pathogen treated months or years previously. This distinction is important because antimicrobial drugs are administered for infection, whereas antiinflammatory agents are needed for inflammation. In the context of PCP, clinical manifestations include shortness of breath, cough, and progressive pulmonary infiltrates, often mimicking an early relapse of PCP.[216]

DIAGNOSIS

PCP should be considered in any immunocompromised patient who develops respiratory symptomatology, fever, and an abnormal chest radiograph. Because this clinical presentation is nonspecific, diagnosis of PCP must be confirmed by demonstration of the organism in a respiratory specimen.

The classic chest radiographic changes are of bilateral diffuse interstitial infiltrates extending from the perihilar region (Fig. 269.5). In early disease the chest radiograph may be normal; with rapidly progressive or late presenting disease, more confluent alveolar shadowing ("white out") with sparing of the costophrenic angles and apices may be seen. Atypical manifestations include unilateral infiltrates, nodules, cystic air spaces, pneumatoceles, mediastinal lymphadenopathy, and effusions.[86,207,217] Of note, patients with nodular granulomas on chest CT have a more indolent onset, less often have PCP seen in BALF, and may require video-assisted thoracoscopic (VATS) or open lung biopsy for diagnosis.[218] In the early years of the HIV pandemic, patients with PCP who were receiving prophylactic aerosolized pentamidine were noted to more likely develop apical infiltrates (mimicking tuberculosis) and pneumothoraces; both these presentations are now rarely encountered with the decline in use of aerosolized pentamidine.[219] Although the chest radiograph is a sensitive way of detecting PCP, it is nonspecific as these radiographic appearances can also occur in other fungal, mycobacterial, and bacterial infections, and in noninfectious conditions, such as interstitial pneumonitis and pulmonary Kaposi sarcoma.

High-resolution CT (HRCT) is important in the evaluation of symptomatic patients with normal or equivocal chest radiographs. Patches of "ground-glass" shadowing are typical for PCP but are also seen in viral (e.g., cytomegalovirus [CMV], influenza A virus) and fungal pneumonia, as well as in occult alveolar hemorrhage.[207] Nuclear medicine imaging using gallium-67 citrate, indium 111,[125] human polyclonal IgG, and technetium 113–labeled monoclonal antibody to *Pneumocystis* Msg demonstrates intrapulmonary accumulation in PCP; these techniques currently have no role in the evaluation of suspected PCP.[220,221]

FIG. 269.5 Chest radiograph. Shown are bilateral infiltrates of *Pneumocystis* pneumonia. *(Courtesy R. Miller.)*

Impaired blood oxygenation is the most frequent laboratory abnormality found in PCP; analysis of the magnitude of hypoxemia or a widened PAO_2-PaO_2 gradient can be used to evaluate disease severity and monitor progression.[202] Lack of exercise-induced arterial desaturation in a symptomatic patient with a normal PaO_2 at rest and a normal or near-normal chest radiograph virtually excludes a diagnosis of PCP.

Elevated serum lactic dehydrogenase (LDH) levels, reflecting lung injury, occur frequently in PCP and decline with successful therapy. However, the usefulness of serum LDH is limited because elevations can be produced by other pulmonary diseases, including pulmonary embolism; nonspecific interstitial pneumonitis; histoplasmosis; extrapulmonary disease, including multicentric Castleman disease; and lymphoma.[222]

Measurement of serum or plasma BG, a component of many fungal cell walls, including *Pneumocystis,* is increasingly being used as an adjunctive diagnostic tool for diagnosis of PCP. BG levels are higher among both HIV-infected and HIV-uninfected patients with PCP, when compared with symptomatic patients with confirmed alternative diagnoses, including aspergillosis and histoplasmosis. There are no clinical trials using BG for diagnosis of *Pneumocystis* pneumonia, but three meta-analyses of clinical evaluations have been reported.[223] Overall, sensitivity is between 90.8% and 94.8%. The sensitivity of BG may be better in HIV-infected patients with *Pneumocystis*, compared with non–HIV-infected patients, likely a consequence of the greater burden of organisms in HIV-infected persons with *Pneumocystis* pneumonia, compared to those with other causes of immunosuppression. Specificity is not as good, ranging between 78.1% and 86.3%, and may also be affected by noninfective factors. False-positive results have been reported in patients with bacterial pneumonia, those undergoing hemodialysis, or those who recently received intravenous (IV) Ig. Positive- and negative-predictive values (NPVs) range between 46.0% and 54.3%, and 97.2% and 99.0%, respectively.[223] These results imply that a negative BG can be used to exclude PCP; however, false-negative results have been reported. Used alone, a positive BG is not diagnostic of *Pneumocystis* pneumonia as this patient population is susceptible to a wide range of fungal pathogens. The clinician should interpret a positive BG result

in the context of compatible imaging findings and, ideally, a positive result from a *Pneumocystis*-specific assay, for instance, histochemical or molecular detection by PCR. By contrast to serum/plasma, BG has poor clinical utility when applied to respiratory samples, such as BALF.[224]

Pneumocystis is rarely identified in spontaneously expectorated sputum. Induced sputum, that is, "induced" by inhalation of an aerosol of hypertonic saline, is a useful screening technique. The diagnostic yield from induced sputum ranges from <50% to >90% at different medical centers.[222] Supervision of the procedure by an experienced respiratory therapist or nurse increases the yield; a negative result for *Pneumocystis* from sputum induction should prompt referral for bronchoscopy.

Fiberoptic bronchoscopy with BAL has a diagnostic yield of >90% for detection of PCP.[86,225] BAL specimens are usually obtained instead of washings and brushings because they have greater sensitivity and low morbidity. The diagnostic yield of BAL specimens can be increased if multiple lobes are sampled or the procedure is directed toward the sites of greatest radiographic abnormality[226]; BAL specimens also provide information that cannot be obtained from induced sputum—about *Pneumocystis* organism burden, the presence of other infectious agents, and the host inflammatory response.[227] Transbronchial biopsy is associated with complications, including pneumothorax and hemorrhage, and provides little additional diagnostic yield; thus it is not routinely performed in the diagnostic workup of suspected PCP. Treatment should not be deferred in any person with suspected PCP when results of bronchoscopy are pending because significant clinical deterioration may occur. The yield for diagnosis of PCP from BALF in HIV-infected individuals is not reduced for up to 14 days after starting treatment; in those with non–HIV-associated PCP, the diagnostic yield may be reduced within a few days of starting treatment.

Open lung biopsy was the standard procedure for the diagnosis of *Pneumocystis* before the introduction of BAL and transbronchial biopsy because it provided the greatest amount of tissue.[86] Open lung biopsy has largely been superseded by VATS lung biopsy. Lung biopsy is indicated in a patient with suspected PCP when bronchoscopy is nondiagnostic and among patients whose clinical course is at variance with laboratory-confirmed PCP, for instance, in evaluating another infection or condition complicating PCP.

One approach to the management of patients with suspected PCP is presented in Fig. 269.6. Patients with a compatible clinical picture and a chest radiograph demonstrating ground-glass opacities should undergo a diagnostic procedure (sputum induction or BAL) to collect respiratory secretions to detect the organism. In symptomatic patients with a normal chest radiograph, additional testing should be performed to assess the probability of early *Pneumocystis* infection. Either thoracic HRCT scanning or pulmonary function testing can identify patients unlikely to have PCP and who may be monitored without specific anti-*Pneumocystis* treatment. One prospective study showed that a normal, unchanged, or equivocal chest radiograph, together with a chest HRCT scan without ground-glass opacities, ruled out PCP.[228] Similarly, a normal or unchanged chest radiograph and a single-breath diffusing capacity for carbon monoxide (DL_{CO}) of >75% of predicted almost rules out the diagnosis of PCP.[229] A DL_{CO} of <75% of predicted has a low specificity, and patients with ground-glass opacities on HRCT (Fig. 269.7) or a DL_{CO} of <75% of predicted need a diagnostic workup to identify *Pneumocystis* or determine an alternative diagnosis.

A variety of stains have been used to identify *Pneumocystis* in respiratory tract secretions; in the hands of an experienced laboratory team, all have a high diagnostic yield for detection of the organism.[86,225,230] GMS stain or one of its simpler variants (e.g., toluidine blue O, cresyl violet), which selectively stain the wall of the *Pneumocystis* cystic form, are widely used because they are easy to interpret. Stains such as Wright-Giemsa or one of its more rapid variants (e.g., Diff-Quik) stain the nuclei of all *Pneumocystis* developmental stages. Calcofluor white is a chemifluorescent agent that binds to cellulose and chitin in the wall of *Pneumocystis* and other fungi. The Papanicolaou stain is a sensitive method to detect the foamy eosinophilic material surrounding *Pneumocystis,* although individual organisms do not stain well. Many laboratories use a rapid staining technique to screen for *Pneumocystis,* which is then followed by a more labor-intensive procedure for definitive identification.

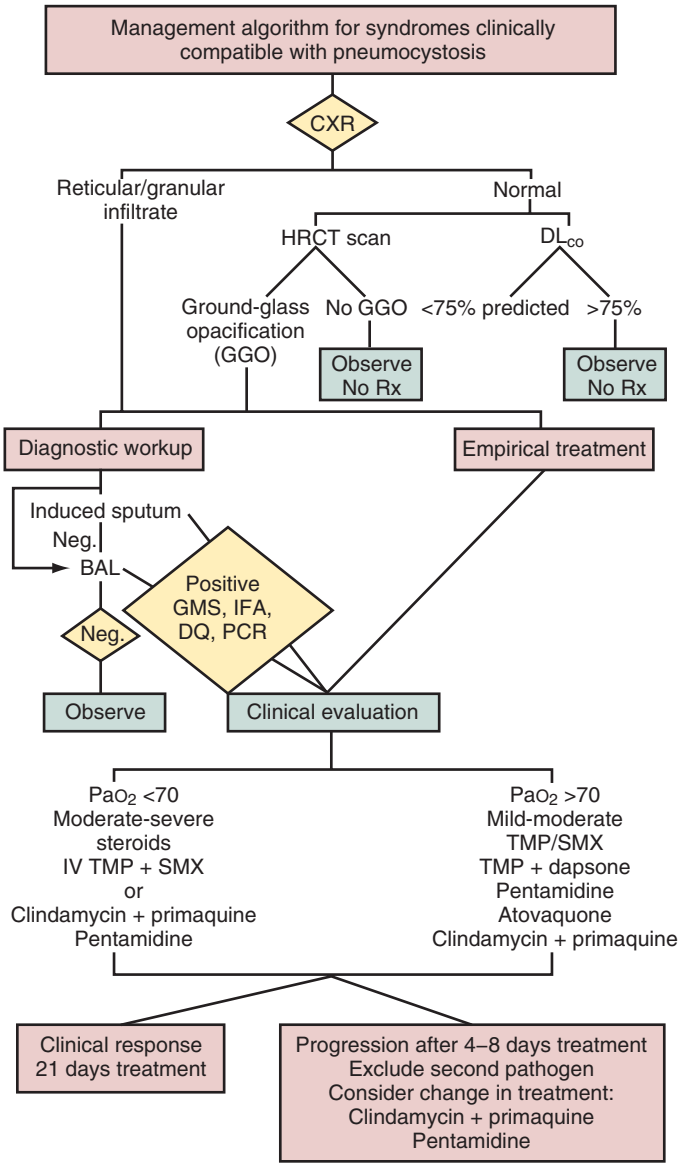

FIG. 269.6 Algorithm for the diagnostic evaluation and management of patients with suspected *Pneumocystis* pneumonia. *BAL,* Bronchoalveolar lavage; *CXR,* chest x-ray; *DL_{CO},* single-breath diffusing capacity for carbon monoxide; *DQ,* Diff-Quik (stain); *GMS,* Grocott-Gomori methenamine silver (stain); *HRCT,* high-resolution computed tomography; *IFA,* immunofluorescent antibody (stain); *IV,* intravenous; *neg.,* negative; *PaO_2,* partial pressure of arterial blood oxygen, *PCR,* polymerase chain reaction; *Rx,* treatment; *TMP/SMX,* trimethoprim-sulfamethoxazole.

Commercial kits using immunofluorescence monoclonal antibodies are more sensitive than histochemical stains in detecting *Pneumocystis*.[230,231] Soluble *Pneumocystis* antigens have been found in patients with PCP by immunoblotting.[232]

Amplification of *Pneumocystis* DNA from respiratory samples by PCR has high sensitivity for *Pneumocystis* detection. Meta-analyses show sensitivity is between 97% and 99%, and the positive likelihood ratio ≥9.9; specificity is moderate to good (between 90% and 94%). In addition, a negative result may help in excluding *Pneumocystis* pneumonia (NPV ≤99%, negative likelihood ratio ≤0.03).[223,233–235] Detection of *Pneumocystis* DNA using PCR in BALF and induced sputum is superior to histolochemical staining for detection of PCP. PCR applied to BALF or induced sputum is increasingly used in the United States and Europe for diagnosis of PCP. Currently available commercial assays (*Pneumocystis jirovecii [carinii]*–FRT PCR kit; AmpliSens), real-time PCR *Pneumocystis jirovecii* (Bio-Evolution; Bry-sur-Marne, France), and MycAssay *Pneumocystis*

FIG. 269.7 High-resolution computed tomography (HRCT) scan of patient with human immunodeficiency virus with *Pneumocystis* pneumonia. This patient had a normal chest radiograph. The HRCT scan demonstrates the characteristic ground-glass opacities. *(Courtesy R. Miller.)*

(Myconostica; South Manchester, United Kingdom), appear to have very similar sensitivity and specificity.

Pneumocystis DNA may also be detected in noninvasive samples, for instance, oropharyngeal gargle samples in individuals presenting with PCP. The specificity and clinical significance of molecular detection assays is limited by the finding of *Pneumocystis* DNA in respiratory samples (BALF, induced sputum, or gargle) from immunosuppressed/deficient patients without respiratory symptoms and in symptomatic persons without PCP (and with a confirmed alternative diagnosis), who are colonized with *Pneumocystis*. The clinical significance of detecting *Pneumocystis* DNA (representing colonization) in a respiratory sample from an immunosuppressed/immunodeficient person in the absence of respiratory symptoms or other confirmatory tests is unclear. Use of real-time quantitative PCR has been used to attempt to differentiate *Pneumocystis* pneumonia from colonization, using the fungal burden based on the PCR cycle threshold. However, this strategy is currently unable to reliably discriminate between *Pneumocystis* pneumonia and colonization. By contrast with respiratory specimens, results from PCR for detection of *Pneumocystis* in blood have been inconsistent.

Pneumocystis lacks *S*-adenosylmethionine (SAM) synthetase and is unable to metabolize SAM, or Adomet; thus it "scavenges" this enzyme from the human host. Measurement of plasma AdoMet concentrations has been proposed as a sensitive test for PCP.[236] In laboratory animal studies AdoMet is depleted in *Pneumocystis*-infected animals. One study of HIV-infected patients with PCP demonstrated lower blood AdoMet levels compared with bacterial or mycobacterial pneumonia. By contrast, overlapping AdoMet levels were described in patients with PCP and with other causes of pneumonia.[237] Currently, measurement of plasma AdoMet levels lacks clinical utility. Serologic tests using crude *Pneumocystis* antigens lack sufficient sensitivity and specificity to be of clinical value.

The collection of specimens that accurately reflect the disease process in lungs is an essential component of the diagnostic evaluation of patients with suspected PCP. The collection procedures used in adults can usually be performed in children, although infants present special problems.[238] In general, more invasive procedures have better diagnostic yields. These procedures usually have a higher diagnostic yield in HIV-infected patients than in those with other causes of immunocompromise because of the higher organism burden in the former group. Since the onset of the HIV pandemic, PCP has placed a strain on health care facilities. One way to reduce costs has been to replace invasive diagnostic procedures with algorithms and simple diagnostic techniques that are predictive of PCP (see Fig. 269.6).[207,225,229,239] A significant problem with clinicians using this approach is that no test can reliably distinguish *Pneumocystis* infection from many other infectious and noninfectious causes of pulmonary infiltrates in the immunosuppressed/deficient patient.

Another way to lower costs has been to use empirical therapy.[240,241] This approach may be pragmatic and appropriate in developing countries without ready access to expensive investigations. In the United States, historically this diagnostic approach results in higher mortality than in patients with a laboratory diagnosis of PCP. Recent studies suggest that empirical therapy may be a cost-effective approach.[242,243] Of note, use of empirical therapy may adversely impact later attempts at establishing a specific causative diagnosis.[244]

GRANULOMATOUS PNEUMOCYSTOSIS

Identifying *P. jirovecii* in GMS stains of respiratory samples is usually straightforward because the cysts collapse readily, appearing as a cluster of helmet, crescent, or spherical nonbudding cells. If lung tissue is seen, cysts are in a frothy mass of eosinophilic material in alveoli. In a small percentage of patients with HIV or hematologic malignancy, cysts are in a necrotic area surrounded by palisades of epithelioid cells and a few giant cells, very much resembling histoplasmosis. Chest CT is atypical for pneumocystosis, showing a reticulonodular pattern or one or a few rounded dense masses, also very compatible with histoplasmosis. These patients often require biopsy for diagnosis because BAL for PCP is negative. Histoplasma in necrotizing granuloma rarely are budding and *Pneumocystis* cells may be sparse and not obviously collapsed. This clinically important distinction can be aided if dark rounded structures are seen in some of the cysts or immunofluorescent stain for *Pneumocystis* is available (Fig. 269.8).

COURSE AND PROGNOSIS

Untreated, the natural history of untreated PCP is characterized by progressive respiratory insufficiency, leading to death. At the time of presentation, an assessment of PCP severity should be made using the results of arterial blood gas estimations. A PaO_2 of >70 mm Hg (9.3 KpA; while breathing room air) indicates mild PCP, and <70 mm Hg (9.3 KpA) indicates severe disease.[202] The severity of PCP can be classified as mild (<35 mm Hg), moderate (35–45 mm Hg), and severe (>45 mm Hg) when expressed as the PAO_2-PaO_2 gradient.

In the first few days of treatment of PCP, patients frequently experience a deterioration in their clinical condition, with worsening chest radiographic findings and oxygenation. This likely arises from either the host inflammatory response to dying *Pneumocystis* or because of *Pneumocystis*-induced changes in surfactant, resulting in worsening lung injury and gas exchange. This phenomenon has only been described in HIV-infected patients with PCP and as such may reflect the lower organism burden in these individuals.

Patients with mild PCP may be treated in an ambulatory care setting, under close clinical supervision. Patients with moderate-to-severe PCP should be treated with IV therapy and adjunctive corticosteroids. Any patient not responding by 4 to 8 days should be switched to alternative therapy. Before ascribing deterioration to treatment failure and considering a change in therapy, evaluation for alternative causes should be done (Table 269.2). In those with an empirical diagnosis, bronchoscopy with BAL should be performed.

All hypoxemic patients with PCP should receive supplemental oxygen delivered via a tight-fitting facemask, to maintain the PaO_2 at ≥60 mm Hg (8.0 KpA). If an inspired oxygen concentration of 60% fails to maintain the PaO_2 at ≥60 mm Hg, escalation of respiratory support should be considered and referral to the intensive care unit (ICU) for noninvasive ventilation or intubation, and mechanical ventilation should be made.

Among HIV-infected patients with severe PCP, prognosis has improved in recent years and is not due to the availability of ART. Rather, the improvements likely reflect the general improvements in ICU management of respiratory failure, including use of low tidal volume ventilation for all-cause acute lung injury, irrespective of HIV status or etiology. Recent reports describe successful outcomes from using extracorporeal membrane oxygenation in refractory hypoxemia caused by PCP.[245]

The overall outcome for HIV-infected patients with PCP has also improved over the past 30 years. Likely, this is due to a combination of factors, including earlier detection of disease, timely institution of treatment, and more effective management of complications. In studies from both the United States and the United Kingdom in the ART era, mortality from PCP is about 10% to 12%.[246,247] By contrast, mortality

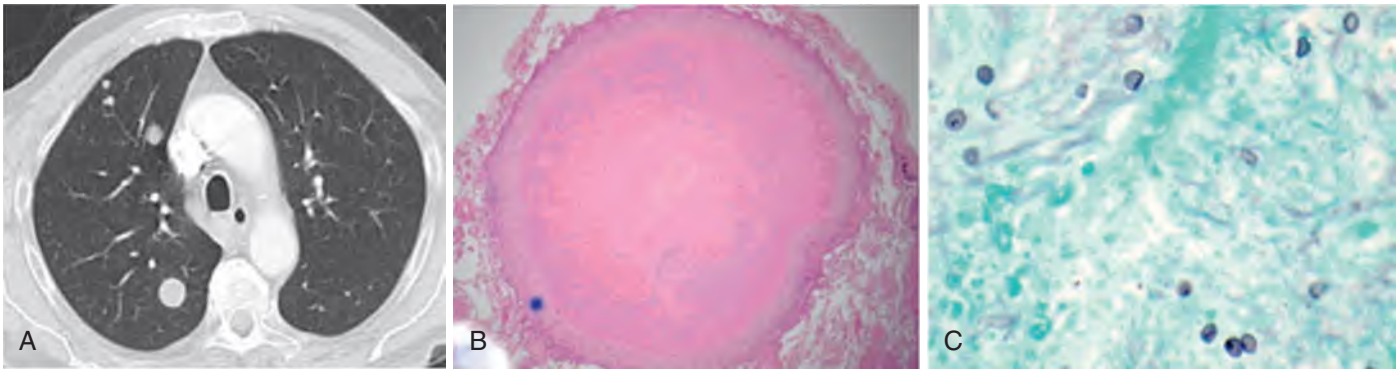

FIG. 269.8 Granulomatous pneumocystosis. (A) Nodules on chest CT. (B) open lung biopsy showing necrotizing granuloma. (C) Grocott-Gomori methenamine silver stain showing cup-shaped cysts, some with a central dot-like or comma-shaped structure (see *arrow*). *(From Kumar N, Bazari J, Rhodes A, Chua F, Tinwell B. Chronic* Pneumocystis jiroveci *presenting as asymptomatic granulomatous pulmonary nodules in lymphoma.* J Infection *2011;62:484–486.)*

TABLE 269.2 Causes of Deterioration in a Patient Receiving Treatment for PCP

ETIOLOGY	EXPLANATION
Severe Progressive PCP	
Iatrogenic	Pulmonary edema due to IV fluid overload when giving TMP-SMX IRIS after early initiation of ART
Side effects of therapy	Anemia (e.g., caused by TMP-SMX), methemoglobinemia (e.g., caused by dapsone, primaquine)
Inadequate therapy	Incorrect dosage or route of administration Adjuvant glucocorticoids not given for treatment of moderate or severe PCP
Postbronchoscopy	Sedation Pneumothorax
Pneumothorax	Spontaneous Associated with intubation and positive pressure ventilation
Copathology in lung	Bacterial infection Pulmonary Kaposi sarcoma Intercurrent pulmonary embolism
Wrong diagnosis	Empirical diagnosis of PCP and correct diagnosis is another pathology (e.g., bacterial pneumonia)

ART, Antiretroviral therapy; *HIV,* human immunodeficiency virus; *IRIS,* immune reconstitution inflammatory syndrome; *IV,* intravenous; *PCP, Pneumocystis* pneumonia; *TMP-SMX,* trimethoprim-sulfamethoxazole.

of PCP among patients with non-HIV PCP remains between 30% and 50%, a figure that has not changed appreciably in more than 2 decades.[135,136,209,248,249] This likely reflects a lack of recognition among clinicians, delay in diagnosis, and thus in starting treatment.

Several clinical and laboratory factors have been shown to predict a poor outcome among HIV-infected patients with PCP at clinical presentation. These include patient age, lack of knowledge of HIV serostatus, second or third episode of PCP, poor oxygenation, marked chest radiographic abnormalities, peripheral blood leukocytosis, low hemoglobin, low serum albumin, and raised LDH enzyme levels. Other prognostic factors include identification in BALF of CMV or other copathogens, >5% neutrophilia, or elevated IL-8 levels; transbronchial biopsy evidence of fibrosis and edema; serum LDH enzyme levels that remain elevated despite treatment; the presence of pulmonary Kaposi sarcoma; previous lung damage; identification of extrapulmonary comorbidity; admission to the ICU; high Acute Physiology and Chronic Health Evaluation (APACHE) II score; the need for mechanical ventilation; and development of pneumothorax.

The value of each prognostic score has a potential to inform the clinician about the safe management of patients in ambulatory care/outpatient settings, to expedite hospitalization, and to identify individuals at greatest risk of death and who should thus be considered for transfer to the ICU. Whereas these prognostic scores are derived from large US/UK cohorts of HIV-infected patients with PCP, none have been validated among any other (US/UK) cohorts or in developing-world settings. This reduces their potential clinical utility. In addition, no validated prognostic scoring systems are available to aid decision making by clinicians in the management of non-HIV–associated PCP (either in adults or children), irrespective of the geographic or clinical setting.

Optimal management of PCP depends on prompt diagnosis and institution of therapy. Early in the HIV epidemic, survival of patients with PCP was better at hospitals with greater familiarity with the disease; however, improvement in management has occurred throughout the medical community. Patients who recover from PCP are at risk for developing recurrent episodes of the disease as long as the immunosuppressive conditions persist.[86] HIV-infected patients are much more likely to develop recurrence than non-HIV patients. It is thought that recurrent episodes occurring within 6 months of the first episode are more likely to be relapses, whereas episodes occurring at more than 6 months are more likely to represent a new episode of infection.[250] Early studies found that the prognosis of recurrent episodes of PCP is similar to that of initial episodes, although more recent analyses have shown a worse outcome with subsequent episodes.[246,251]

Pneumothorax may complicate treatment of an episode of PCP.[207,252,253] Pneumothorax is more likely in a recurrent episode of PCP, in those who have received aerosolized pentamidine, and among cigarette smokers. Respiratory support, with positive end-expiratory pressure spontaneous mechanical ventilation, is an independent risk factor. Pneumatoceles, pneumomediastinum, and subcutaneous emphysema also occur. Management is difficult and should be individualized; interventions include chest tube, surgical or chemical pleurodesis, and thoracotomy with pleural stapling or use of adhesive. Prior receipt of corticosteroids may increase morbidity.[252]

TREATMENT

Recommendations for the treatment and prevention presented here are based on the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (Table 269.3).[254,255] Trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for all forms of PCP. This agent, which acts by inhibiting folic acid synthesis, has been used for 4 decades to treat *Pneumocystis* with high success rates.[256–259] Among the attractive features of TMP-SMX are its availability in both oral and parenteral forms, well-described pharmacokinetics, antibacterial properties, and cost. The parenteral preparation should be used in

TABLE 269.3 Treatment of *Pneumocystis* Pneumonia

DRUG	DOSE	COMMENTS
Preferred		
TMP-SMX[a]	15–20 mg/kg (TMP) and 75–100 mg/kg (SMX) IV or PO divided into doses given q6–8h (AI)[b]	*Severe PCP*: IV may be switched to PO with clinical improvement *Mild-to-moderate PCP*: PO dose can be given as TMP-SMX DS 2 tablets PO tid
Alternatives		
Clindamycin *plus*	600–900 mg IV q6–8h *or* 300–450 mg PO q6–8h *plus*	*Severe PCP*: IV may be switched PO with clinical improvement *Mild-to-moderate PCP:* PO dose can be used Check for G6PD deficiency before use
Primaquine	15 or 30 mg (of the base) PO qd (BI)	
Pentamidine	4 mg/kg IV q24h (BI)	For moderate-to-severe PCP, some clinicians "dose reduce" to 3 mg/kg to reduce toxicity
TMP *plus*	15 mg/kg PO (in divided doses, q8h) *plus*	For mild-to-moderate PCP, monitor for methemoglobinemia
Dapsone	100 mg PO qd (BI)	
Atovaquone	750 mg suspension PO bid (BI)	For mild-to-moderate PCP, take with food
Adjunctive		
Prednisone	40 mg PO bid days 1–5 40 mg PO qd days 6–10 20 mg PO qd days 11–21 (AI) IV methylprednisolone can be administered as 75% of PO prednisone dose	For moderate-to-severe PCP, PaO_2 ≤70 mm Hg, or alveolar-arterial O_2 gradient >35 mm Hg Begin as soon as possible and within 72 h of starting PCP therapy

[a]DS tablet = TMP 160 mg and SMX 800 mg.
[b]AI and BI grading scores are defined as follows: *AI,* Strong recommendation for the statement: one or more randomized trials with clinical outcomes or validated laboratory end points; *BI,* moderate recommendation for the statement: one or more randomized trials with clinical outcomes or validated laboratory end points.
bid, Twice per day; *DS,* double strength; *G6PD,* glucose-6-phosphate dehydrogenase; *IV,* intravenously; *PaO_2,* partial pressure of arterial blood oxygen; *PCP, Pneumocystis* pneumonia; *PO,* orally; *qd,* every day; *SMX,* sulfamethoxazole; *tid,* three times per day; *TMP,* trimethoprim.
Duration of therapy is 21 days for patients with underlying human immunodeficiency virus infection; shorter treatment course (typically 14–17 days) for those with other causes of immunodeficiency (e.g., renal transplantation).
Modified from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed May 19, 2017.*

patients who are seriously ill or have GI disturbances. As with all anti-*Pneumocystis* drugs, treatment should be continued for 21 days in HIV-positive patients and for at least 14 days in non-HIV patients. The reason for the longer duration in HIV-positive patients is because this patient group has a higher organism burden and responds to treatment more slowly.

TMP-SMX is well tolerated by HIV-uninfected patients, with GI symptoms and skin rashes being the most common adverse events. By contrast, HIV-positive patients experience a high frequency (up to 80% or more) of adverse reactions, which usually begin during the second week of TMP-SMX therapy and may result in discontinuation of the drug in up to 50%.[260,261] Adverse effects of therapy include rash, fever, cytopenias, nausea and vomiting, hepatitis, pancreatitis, nephritis, hyperkalemia, metabolic acidosis, central nervous system manifestations, and an anaphylactoid reaction. Most of these reactions appear to be caused by the sulfonamide component, but the mechanisms are poorly understood. Among the possible contributing factors are elevated serum drug levels, the formation of hydroxylamine metabolites, glutathione deficiency, hypersensitivity, and high CD4 counts.[261–263] Hyperkalemia has been attributed to TMP, which competitively inhibits potassium excretion by distal nephron (acting like amiloride, a potassium-sparing diuretic).[264]

Some clinicians adjust the dosage of TMP-SMX to achieve serum concentrations of 5 to 8 μg/mL TMP and 100 to 150 μg/mL SMX to achieve maximum efficacy and minimum toxicity[258,261]; however, others have not found this approach either beneficial or practical.[265] *N*-acetylcysteine and folinic acid do not prevent side effects from TMP-SMX, and folinic acid may possibly reduce efficacy. Cutaneous reactions to TMP-SMX range from mild to life threatening (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, anaphylaxis). In some cases the rash and manifestations such as fever may resolve spontaneously or respond to conservative measures, whereas in other cases they may require discontinuation of the drug. Oral corticosteroids may also be helpful.[266] Desensitization regimens have been successful in patients who have experienced non–life-threatening reactions to TMP-SMX but should be undertaken with caution.[267]

Several alternative regimens have been developed for the treatment of mild-to-moderate PCP (see Table 269.3). Although these studies have been performed mainly in HIV-infected patients, the results should be applicable to non-HIV patients with PCP. TMP administered orally combined with dapsone orally has been shown to be as effective as TMP-SMX and is less toxic.[268] The major adverse reactions to dapsone are methemoglobinemia, rash, fever, nausea, and vomiting; hemolysis can occur in patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency. Caution is advised in administering dapsone to patients who have been intolerant of sulfonamides. The serum levels of dapsone and TMP are higher when these drugs are used together than when used alone and suggest bidirectional interference with clearance.[269]

Controlled studies have shown that the combination of clindamycin and primaquine has comparable efficacy and toxicity to TMP-SMX and TMP plus dapsone in treatment of PCP.[268,270] The mechanism of action of clindamycin and primaquine against *Pneumocystis* is not known. The usual regimen is shown in Table 269.3. Treatment may also be initiated with IV clindamycin and then switched to oral administration once recovery is evident. Adverse drug reactions to primaquine appear to be less common with use of 15 mg, rather than 30 mg, every day and include rash, fever, neutropenia, GI complaints, and methemoglobinemia.[260] Primaquine also causes hemolysis in patients with G6PD deficiency.

Atovaquone is a hydroxynaphthoquinone originally developed as an antimalarial agent. Atovaquone acts on the mitochondrial electron transport chain of plasmodia and, based on mutations found in *Pneumocystis* isolates from patients for whom atovaquone prophylaxis was not effective, drug targets are similar in *Pneumocystis*. One study compared atovaquone with TMP-SMX and another with IV pentamidine isethionate for the treatment of mild-to-moderate PCP in HIV patients.[271,272] Atovaquone was less effective than TMP-SMX and showed equivalent efficacy to IV pentamidine; however, atovaquone was better tolerated in both studies. Adverse reactions to atovaquone include skin rash, fever, GI symptoms, and abnormal liver function tests. An oral suspension is administered at a dose of 750 mg/5 mL, twice daily with food.[273]

The combination of clindamycin and primaquine is the preferred alternative regimen to TMP-SMX for moderate-to-severe PCP in HIV-positive patients, as shown by a systematic review that also included new data from the authors' patient populations, supporting a previous meta-analysis that reported clindamycin and primaquine is superior to pentamidine as salvage treatment of PCP (i.e., patients who did not respond to first-line treatment of PCP).[274,275] A dose of clindamycin (600–900 mg IV every 6–8 hours) is usually used.[276,277]

Another agent used to treat PCP is pentamidine isethionate, a drug first used to treat African trypanosomiasis.[278] Pentamidine appears to exert its antimicrobial activity by binding to DNA, but its precise mode of action against *Pneumocystis* is unknown. IV pentamidine appears to be almost as effective as TMP-SMX in treatment of PCP in HIV-positive

and non-HIV patients.[256–259] Pentamidine is administered as a single IV daily dosage of 4 mg/kg/day. The drug is diluted in 250 mL of a 5% dextrose solution and infused over a period of at least 1 hour. Aerosolized pentamidine is used in prophylaxis of PCP but has no role in treatment.

Pharmacokinetic studies have shown that IV pentamidine follows a three-compartment model with rapid passage to tissues, secondary distribution, and a long (≈12 days) elimination half-life. Only a small amount of the drug is cleared by the kidney.[261,279] Pentamidine is a toxic drug; adverse reactions occur in 80% or more of HIV-positive and non-HIV patients and are severe enough to necessitate discontinuation of the drug in approximately half of cases. Side effects include hypotension, cardiac arrhythmias (e.g., torsades de pointes), azotemia, pancreatitis, dysglycemias, hyperkalemia, hypomagnesemia, hypocalcemia, neutropenia, hepatic dysfunction, bronchospasm, and problems at intramuscular injection sites. Hypoglycemia, which develops from damage to pancreatic β cells, resulting in insulin release, occurs early in therapy; hypoglycemia may later be followed by secondary diabetes mellitus caused by necrosis of the pancreatic β cells. The frequency of hypoglycemia and azotemia has been correlated with high serum pentamidine levels, total drug dose, and duration of treatment.[278,280] The mechanism of hyperkalemia caused by pentamidine is similar to that caused by TMP.[281]

The response to anti-*Pneumocystis* drugs generally reflects other clinical features of the infection. Most patients show a clinical response after several days of treatment; if there is no response by 4 to 8 days, it is wise to consider switching to another drug. HIV-positive patients typically respond more slowly than non-HIV patients and take longer to clear *Pneumocystis* from their lungs. As noted, clindamycin with primaquine is the preferred regimen for those patients who do not respond to TMP-SMX; conversely, TMP-SMX is the preferred regimen for patients for whom other regimens are not effective.[274] Adding a second anti-*Pneumocystis* drug to the regimen is no more effective than substituting one agent for another and may increase the risk of adverse reactions.

HIV-infected patients with PCP frequently experience worsening of their blood oxygenation during the first few days of therapy; such a clinical deterioration can be particularly dangerous if the initial hypoxemia is marked. Several studies have shown that the administration of corticosteroids during the first 72 hours of treatment can lessen the decline in oxygenation and improve survival. These studies led to a recommendation by an expert panel that steroids be added to the treatment of all patients with moderate-to-severe PCP, that is, an arterial oxygen pressure ≤70 mm Hg (<9.3 kPA) or a PAO_2-PaO_2 gradient >35 mm Hg.[202] The use of "adjunctive" corticosteroids has been widely adopted by the medical community. A meta-analysis and a more recent systematic review support the use of corticosteroids both in reducing mortality and in the need for mechanical ventilation among HIV-infected adults with PCP.[275,282,283] Corticosteroids used in the manner described have generally been well tolerated.[202] The principal side effects are oral candidiasis, mucocutaneous herpes simplex, and metabolic changes such as hyperglycemia. Concerns about an increased frequency of cytomegaloviral, other fungal, and mycobacterial infections have not materialized. Nevertheless, the lack of efficacy shown in some studies,[283,284] as well as the risk of other opportunistic infections and other possible complications (e.g., increased morbidity from pneumothorax, lifetime increased risk of osteoporosis and fracture), emphasize the need for careful patient selection and follow-up.

Recommendations about the use of adjunctive corticosteroids in *Pneumocystis* among patients with other causes of immunosuppression are difficult to formulate because of the lack of data from controlled trials. Studies infer that corticosteroids may speed clinical improvement, but survival results from meta-analyses are conflicting.[285,286] Among non-HIV patients with PCP, most have received corticosteroids shortly before or at the time they developed PCP. Rapid withdrawal of steroids may have serious adverse consequences, and thus it seems prudent either to maintain or increase the steroid dose when instituting anti-*Pneumocystis* therapy. The steroid dose can then be slowly tapered. The place of adjunctive corticosteroids in non-HIV patients who have received immunosuppressive drugs other than steroids at the time of diagnosis of PCP is unknown.

Future clinical advances in the treatment of PCP might come from several current lines of investigation. Although the development of a continuous culture system remains elusive, it might be possible to use molecular techniques to identify markers of virulence or antimicrobial resistance. Sequence variation in the gene encoding dihydropteroate synthetase, the target enzyme of sulfonamides, in human *Pneumocystis* has been identified.[287] These mutations, at positions associated with sulfonamide resistance in other organisms, have been associated with failure in prophylaxis, but no clear association with treatment failure or altered outcome has been demonstrated. A systematic review has shown that patients receiving sulfa drugs for PCP prophylaxis had a significantly higher risk of developing these mutations but concluded that there was not enough evidence that the mutations adversely affected disease outcome.[288] Subsequently, a trend toward more severe disease and worse outcome associated with these mutations has been described in two of three studies.[289–291] Mutations have also been described in the gene encoding cytochrome B and have been associated with failure of atovaquone prophylaxis of PCP.[292]

New drugs with improved efficacy, less toxicity, and different mechanisms of action are needed. Animal models, which are the principal test system, have facilitated identification of several new types of drugs (e.g., echinocandins, 8-aminoquinolines, diamidines); however, data from clinical trials are lacking. A more promising approach has been to investigate drugs that are already licensed for other agents for activity against *Pneumocystis*. Several case series and additional case reports show that echinocandin monotherapy may be effective as salvage in patients with PCP who are not responding to, or intolerant of, first-line therapy. Echinocandins have not been prospectively evaluated against TMP-SMX or other regimens as first-line therapy for PCP and therefore, based on animal studies, their use should only be considered in combination with an additional anti-*Pneumocystis* agent.

Several small studies (largely retrospective case series, and thus potentially susceptible to selection bias) show low-dose TMP-SMX (doses ≤10 mg/kg/day of TMP, with ≤50 mg/kg/day SMX) have shown good treatment outcomes and reduced toxicity. In addition, several case reports describe good outcomes from use of low-dose TMP-SMX with caspofungin. These observations require evaluation in prospective clinical trials before clinicians incorporate them into treatment algorithms.

PREVENTION

There are several methods of preventing PCP: (chemo)prophylaxis, improving immune responses, and reducing exposure.

Chemoprophylaxis

The need for PCP chemoprophylaxis for PCP in HIV-positive patients is widely recognized. Prophylaxis can be considered primary, given to prevent a first episode of PCP, or secondary, given to prevent recurrent episodes. A decision to institute chemoprophylaxis depends on factors including the incidence of PCP in the target population, as well as the efficacy of specific drug regimens, their safety, ease of administration, and cost. As none of the currently available anti-*Pneumocystis* drugs used in humans has a "cidal" activity against *Pneumocystis,* chemoprophylaxis should be continued for as long as the underlying immunosuppressive condition exist.

With progression of HIV infection and decline in the CD4 count, HIV-infected patients are increasingly at risk of developing PCP. *Primary prophylaxis* is given to patients with CD4 lymphocyte counts <200 cells/mm^3, or the proportion of CD4 lymphocytes is <14%; to patients with HIV-related constitutional symptoms, such as unexplained fever (>100°F) for 2 or more weeks' duration; those with oral candidiasis (regardless of CD4 count); and to patients who have other AIDS-defining diagnoses, such as Kaposi sarcoma. *Secondary prophylaxis* is given to prevent a recurrence; indications for secondary prophylaxis are similar to those for primary prophylaxis. Indications of giving chemoprophylaxis to patients with other causes of immunosuppression are shown in Table 269.1.

TMP-SMX is the drug of choice for chemoprophylaxis. Three oral TMP-SMX regimens have similar rates of efficacy; however, single-strength TMP-SMX may have fewer adverse reactions than double-strength TMP-SMX. Rash, with or without fever, occurs in up to 20% of patients. Desensitization should be attempted (with caution) in those

TABLE 269.4 Prevention of *Pneumocystis* Pneumonia

DRUG	DOSE	COMMENTS
Preferred		
TMP-SMX[a]	1 DS tab PO qd (AI)[b] 1 SS tab PO qd (AI)	Both regimens are effective; SS tab may have fewer side effects
Alternative		
TMP-SMX	1 DS tab PO tiw (BI)	Similar to other TMP-SMX regimens
Dapsone	100 mg PO qd (BI) or 50 mg PO bid	Methemoglobinemia may occur
Dapsone *plus*	50 mg PO qd *plus*	Methemoglobinemia may occur
Pyrimethamine *plus*	50 mg PO qwk (BI) *plus*	May also prevent toxoplasmosis
Leucovorin	25 mg PO qwk	
Pentamidine	300 mg qmo aerosolized via Respirgard II nebulizer (BI)	
Atovaquone	750 mg suspension PO bid or 1500 mg qd (BI)	
Atovaquone *plus*	750 mg suspension PO bid or 1500 mg qd *plus*	
Pyrimethamine *plus*	25 mg PO qd (BII) *plus*	
Leucovorin	10 mg PO qd	

[a]SS tablet = TMP 80 mg and SMX 400 mg; DS tablet = TMP160 mg and SMX 800 mg.
[b]AI and BI grading scores are defined as follows: *AI,* Strong recommendation for the statement: one or more randomized trials with clinical outcomes/or validated laboratory end points; *BI,* moderate recommendation for the statement: one or more randomized trials with clinical outcomes/or validated laboratory end points; *BII,* moderate recommendation for the statement: one or more well-designed, nonrandomized trials, or observational cohort studies with long-term clinical outcomes.
bid, Twice per day; *DS,* double strength; *qd,* every day; *qmo,* every month; *qwk,* every week; *PO,* orally; *SS,* single strength; *tiw,* three times per week; *TMP-SMX,* trimethoprim-sulfamethoxazole.
Modified from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_0i.pdf. Accessed May 19, 2017.*

unable to tolerate TMP-SMX when used as prophylaxis. Guidelines for desensitization or rechallenge with TMP-SMX for prophylaxis are similar to those for use of TMP-SMX in treatment.

Recommended chemoprophylaxis regimens for patients who cannot tolerate TMP-SMX include dapsone, aerosolized pentamidine, and atovaquone. Dapsone may be administered alone or in combination with pyrimethamine and leucovorin (Table 269.4). Additional dosage schedules have also been used. Overall, dapsone-containing regimens show inferior efficacy but equivalent toxicity to TMP-SMX regimens. Both dapsone and pyrimethamine additionally protect against *Toxoplasma gondii* but not against bacterial infections. Atovaquone has similar efficacy to dapsone in patients intolerant of TMP-SMX. Pentamidine is administered at a dose of 300 mg, delivered via Vital Signs Respirgard II nebulizer (Vital Signs/Vitality Medical; Salt Lake City, UT) once monthly. Other delivery systems cannot be recommended. Aerosolized pentamidine is less effective, better tolerated, and much more expensive than TMP-SMX or dapsone. Major side effects include cough and bronchospasm, which can be controlled by use of a β-agonist. Administration of aerosolized pentamidine in a health care setting requires a negative-pressure room with adequate ventilation and should not be administered to patients with suspected/proven smear-positive tuberculosis because of the risks of nosocomial transmission. A number of other drug regimens have been considered possible *Pneumocystis* prophylactic agents, but there is insufficient supportive information to recommend their use. Intermittent IV pentamidine used as prophylaxis is inferior to all other regimens and cannot be recommended for use by clinicians.

Stopping Prophylaxis

In the late 1990s the widespread availability and uptake of ART by patients in the United States, Europe, and Australasia resulted in marked reductions in the incidence of many opportunistic infections, including PCP, hospital admissions, and mortality from HIV infection. In a majority of patients, within a few weeks of starting ART rapid reductions in plasma HIV RNA occur; these parallel increases in peripheral blood CD4 counts. Primary *Pneumocystis* prophylaxis should be discontinued for patients who after starting ART have an increase in CD4 counts from <200 cells/mm^3 to >200 cells/mm^3 maintained for more than 3 months. Discontinuing primary prophylaxis in this patient group is recommended because its preventive benefits against PCP are limited, and stopping prophylaxis additionally reduces the potential for adverse drug reactions, drug-drug interactions, selection of drug-resistance, as well as reducing pill burden and health care costs. Prophylaxis should be reintroduced if the CD4 count decreases to <200 cells/mm^3.

The incidence of PCP in patients receiving ART and with CD4 counts between 100 and 200 cells/mm^3, who have HIV viral loads between <50 and 400 copies/mL, and who stop or never receive PCP prophylaxis is low.[254] This observation suggests that both primary and secondary PCP prophylaxis can be safely discontinued in patients with CD4 counts between 100 and 200 cells/mm^3 and HIV plasma RNA levels that are below limits of detection (<50 copies/mL).

Prophylaxis of PCP Among Patients With Non–HIV-Associated Immunosuppression

Recent reviews and guidelines have better defined the need and prophylactic regimens indicated to prevent PCP in non–HIV-infected individuals. The indications for prophylaxis and recommended regimens are shown in Table 269.1.

Boosting Host Immune Response

Manipulation of the host innate or adaptive immune response could improve defenses against *Pneumocystis* while lessening their deleterious effects on the host.[293] An example of this principle is the use of an anti-CD3 antibody in an animal model of PCP.[294] These studies might lead to the development of drugs with greater specificity than corticosteroids. Immunization of immunocompromised patients at an early stage of their disease, for example, HIV patients with a CD4 count >500 cells/mm^3 or newly diagnosed cancer patients, might prevent, delay, or lessen the severity of PCP. Boosting the host immune response might also lessen the need for, or lower the dosage of, antimicrobial drugs. A promising antigen with the potential to achieve these objectives is the Kex antigen, which contains protective B-cell and T-cell epitopes; immunization with Kex to CD4-depleted mice protects against PCP.[104] Clinical trials of a Kex vaccine are needed as there is no evidence of protective effect in humans.

Preventing Exposure

A third method of preventing PCP is by preventing or reducing exposure. There is accumulating evidence showing *Pneumocystis* is transmissible in both humans and experimental animal models. Although *Pneumocystis* can be quantified in the air near patients with PCP—and multiple outbreaks have been described in kidney transplant patients, each caused by distinct strains of *Pneumocystis*—data that strongly suggest high-risk immunocompromised patients without PCP may benefit from isolation from other patients with known PCP infection in health care settings nonetheless are currently insufficient to support isolation as routine practice.[254]

Little is known about the effects of environmental factors on the viability of *Pneumocystis* outside of its host. In animal models *Pneumocystis* cysts derived from mice are susceptible to most common disinfectants, except 0.5% hypochlorous acid.[295] *Pneumocystis* cystic forms obtained from rats can be stored at −80°C for several months yet maintain their viability and are able to infect other mice and rats.[296]

Key References

The complete reference list is available online at Expert Consult.

1. Skalski JH, Kottom TJ, Limper AH. Pathobiology of *Pneumocystis* pneumonia: life cycle, cell wall and cell signal transduction. *FEMS Yeast Res*. 2015;15.
5. Wickramasekaran RN, Jewell MP, Sorvillo F, et al. The changing trends and profile of pneumocystosis mortality in the United States, 1999-2014. *Mycoses*. 2017;60:607–615.
7. Ma L, Chen Z, Huang da W, et al. Genome analysis of three *Pneumocystis* species reveals adaptation mechanisms to life exclusively in mammalian hosts. *Nat Commun*. 2016;7:10740.
11. Redhead SA, Cushion MT, Frenkel JK, et al. *Pneumocystis* and *Trypanosoma cruzi:* nomenclature and typifications. *J Eukaryot Microbiol*. 2006;53:2–11.
17. Almeida JM, Cisse OH, Fonseca A, et al. Comparative genomics suggests primary homothallism of *Pneumocystis* species. *MBio*. 2015;6.
18. Cushion MT, Linke MJ, Ashbaugh A, et al. Echinocandin treatment of *Pneumocystis* pneumonia in rodent models depletes cysts leaving trophic burdens that cannot transmit the infection. *PLoS ONE*. 2010;5:e8524.
20. Kaneshiro ES. Sterol metabolism in the opportunistic pathogen *Pneumocystis:* advances and new insights. *Lipids*. 2004;39:753–761.
21. Hauser PM, Burdet FX, Cisse OH, et al. Comparative genomics suggests that the fungal pathogen *Pneumocystis* is an obligate parasite scavenging amino acids from its host's lungs. *PLoS ONE*. 2010;5:e15152.
23. De Stefano JA, Myers JD, Du Pont D, et al. Cell wall antigens of *Pneumocystis carinii* trophozoites and cysts: purification and carbohydrate analysis of these glycoproteins. *J Eukaryot Microbiol*. 1998;45:334–343.
25. Porollo A, Meller J, Joshi Y, et al. Analysis of current antifungal agents and their targets within the *Pneumocystis carinii* genome. *Curr Drug Targets*. 2012;13:1575–1585.
26. Cushion MT, Collins MS, Sesterhenn T, et al. Functional characterization of *Pneumocystis carinii* inositol transporter 1. *MBio*. 2016;7.
27. Stringer JR. Antigenic variation in *Pneumocystis*. *J Eukaryot Microbiol*. 2007;54:8–13.
29. Gigliotti F, Hughes WT. Passive immunoprophylaxis with specific monoclonal antibody confers partial protection against *Pneumocystis carinii* pneumonitis in animal models. *J Clin Invest*. 1988;81:1666–1668.
33. Ezekowitz RA, Williams DJ, Koziel H, et al. Uptake of *Pneumocystis carinii* mediated by the macrophage mannose receptor. *Nature*. 1991;351:155–158.
37. O'Riordan DM, Standing JE, Kwon KY, et al. Surfactant protein D interacts with *Pneumocystis carinii* and mediates organism adherence to alveolar macrophages. *J Clin Invest*. 1995;95:2699–2710.
39. Kutty G, Ma L, Kovacs JA. Characterization of the expression site of the major surface glycoprotein of human-derived *Pneumocystis carinii*. *Mol Microbiol*. 2001;42:183–193.
40. Schmid-Siegert E, Richard S, Luraschi A, et al. Mechanisms of surface antigenic variation in the human pathogenic fungus *Pneumocystis jirovecii*. *MBio*. 2017;8.
42. Walzer PD, Djawe K, Levin L, et al. Long-term serologic responses to the *Pneumocystis jirovecii* major surface glycoprotein in HIV-positive individuals with and without *P. jirovecii* infection. *J Infect Dis*. 2009;199:1335–1344.
44. Tipirneni R, Daly KR, Jarlsberg LG, et al. Healthcare worker occupation and immune response to *Pneumocystis jirovecii*. *Emerg Infect Dis*. 2009;15:1590–1597.
45. Schaffzin JK, Sunkin SM, Stringer JR. A new family of *Pneumocystis carinii* genes related to those encoding the major surface glycoprotein. *Curr Genet*. 1999;35:134–143.
47. Gigliotti F, Haidaris CG, Wright TW, et al. Passive intranasal monoclonal antibody prophylaxis against murine *Pneumocystis carinii* pneumonia. *Infect Immun*. 2002;70:1069–1074.
52. Montes-Cano MA, Chabe M, Fontillon-Alberdi M, et al. Vertical transmission of *Pneumocystis jirovecii* in humans. *Emerg Infect Dis*. 2009;15:125–127.
53. Vargas SL, Hughes WT, Santolaya ME, et al. Search for primary infection by *Pneumocystis carinii* in a cohort of normal, healthy infants. *Clin Infect Dis*. 2001;32:855–861.
54. Larsen HH, von Linstow ML, Lundgren B, et al. Primary *Pneumocystis* infection in infants hospitalized with acute respiratory tract infection. *Emerg Infect Dis*. 2007;13:66–72.
60. Davis JL, Welsh DA, Beard CB, et al. *Pneumocystis* colonisation is common among hospitalised HIV infected patients with non-*Pneumocystis* pneumonia. *Thorax*. 2008;63:329–334.
61. Shipley TW, Kling HM, Morris A, et al. Persistent *Pneumocystis* colonization leads to the development of chronic obstructive pulmonary disease in a non human primate model of AIDS. *J Infect Dis*. 2010;202:302–312.
62. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med*. 1981;305:1431–1438.
64. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000-2010. *J Infect Dis*. 2016;214:862–872.
65. Lowe DM, Rangaka MX, Gordon F, et al. *Pneumocystis jirovecii* pneumonia in tropical and low and middle income countries: a systematic review and meta-regression. *PLoS ONE*. 2013;8:e69969.
68. de Boer MG, Kroon FP, le Cessie S, et al. Risk factors for *Pneumocystis jirovecii* pneumonia in kidney transplant recipients and appraisal of strategies for selective use of chemoprophylaxis. *Transpl Infect Dis*. 2011;13:559–569.
69. Maertens J, Cesaro S, Maschmeyer G, et al. ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother*. 2016;71:2397–2404.
70. Wolfe RM, Peacock JE Jr. *Pneumocystis* pneumonia and the rheumatologist: which patients are at risk and how can PCP be prevented? *Curr Rheumatol Rep*. 2017;19:35.
74. Dohn MN, White ML, Vigdorth EM, et al. Geographic clustering of *Pneumocystis carinii* pneumonia in patients with HIV infection. *Am J Respir Crit Care Med*. 2000;162:1617–1621.
75. Morris AM, Swanson M, Ha H, et al. Geographic distribution of human immunodeficiency virus-associated *Pneumocystis carinii* pneumonia in San Francisco. *Am J Respir Crit Care Med*. 2000;162:1622–1626.
76. Miller RF, Evans HE, Copas AJ, et al. Climate and genotypes of *Pneumocystis jirovecii*. *Clin Microbiol Infect*. 2007;13:445–448.
77. Djawe K, Levin L, Swartzman A, et al. Environmental risk factors for *Pneumocystis pneumonia* hospitalizations in HIV patients. *Clin Infect Dis*. 2013;56:74–81.
79. Icenhour CR, Rebholz SL, Collins MS, et al. Widespread occurrence of *Pneumocystis carinii* in commercial rat colonies detected using targeted PCR and oral swabs. *J Clin Microbiol*. 2001;39:3437–3441.
80. de Boer MG, de Fijter JW, Kroon FP. Outbreaks and clustering of *Pneumocystis* pneumonia in kidney transplant recipients: a systematic review. *Med Mycol*. 2011;49:673–680.
81. Choukri F, Menotti J, Sarfati C, et al. Quantification and spread of *Pneumocystis jirovecii* in the surrounding air of patients with *Pneumocystis* pneumonia. *Clin Infect Dis*. 2010;51:259–265.
84. Gingo MR, Lucht L, Daly KR, et al. Serologic responses to *Pneumocystis* proteins in HIV patients with and without *Pneumocystis jirovecii* pneumonia. *J Acquir Immune Defic Syndr*. 2011;57:190–196.
89. Porollo A, Sesterhenn TM, Collins MS, et al. Comparative genomics of *Pneumocystis* species suggests the absence of genes for myo-inositol synthesis and reliance on inositol transport and metabolism. *MBio*. 2014;5:e01834.
90. Koziel H, Kim S, Reardon C, et al. Enhanced in vivo human immunodeficiency virus-1 replication in the lungs of human immunodeficiency virus-infected persons with *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med*. 1999;160:2048–2055.
91. Limper AH, Edens M, Anders RA, et al. *Pneumocystis carinii* inhibits cyclin-dependent kinase activity in lung epithelial cells. *J Clin Invest*. 1998;101:1148–1155.
93. Hoving JC, Kolls JK. New advances in understanding the host immune response to *Pneumocystis*. *Curr Opin Microbiol*. 2017;40:65–71.
94. Linke MJ, Harris CE, Korfhagen TR, et al. Immunosuppressed surfactant protein A-deficient mice have increased susceptibility to *Pneumocystis carinii* infection. *J Infect Dis*. 2001;183:943–952.
100. de la Rua NM, Samuelson DR, Charles TP, et al. CD4(+) T-Cell-independent secondary immune responses to *Pneumocystis* pneumonia. *Front Immunol*. 2016;7:178.
101. Kling HM, Shipley TW, Patil SP, et al. Relationship of *Pneumocystis jiroveci* humoral immunity to prevention of colonization and chronic obstructive pulmonary disease in a primate model of HIV infection. *Infect Immun*. 2010;78:4320–4330.
103. Garvy BA, Wiley JA, Gigliotti F, et al. Protection against *Pneumocystis carinii* pneumonia by antibodies generated from either T helper 1 or T helper 2 responses. *Infect Immun*. 1997;65:5052–5056.
104. Zheng M, Ramsay AJ, Robichaux MB, et al. CD4+ T cell-independent DNA vaccination against opportunistic infections. *J Clin Invest*. 2005;115:3536–3544.
105. Zheng M, Rapaka RR, Yu AC, et al. Role of interleukin-23-dependent antifungal immune responses in dendritic cell-vaccinated mice. *Infect Immun*. 2011;79:3778–3783.
106. Tesini BL, Wright TW, Malone JE, et al. Immunization with *Pneumocystis* cross-reactive antigen 1 (Pca1) protects mice against *Pneumocystis* pneumonia and generates antibody to *Pneumocystis jirovecii*. *Infect Immun*. 2017;85.
112. Blount RJ, Daly KR, Fong S, et al. Effects of clinical and environmental factors on bronchoalveolar antibody responses to *Pneumocystis jirovecii*: a prospective cohort study of HIV+ patients. *PLoS ONE*. 2017;12:e0180212.
114. Shellito J, Suzara VV, Blumenfeld W, et al. A new model of *Pneumocystis carinii* infection in mice selectively depleted of helper T lymphocytes. *J Clin Invest*. 1990;85:1686–1693.
101. Theus SA, Andrews RP, Steele P, et al. Adoptive transfer of lymphocytes sensitized to the major surface glycoprotein of *Pneumocystis carinii* confers protection in the rat. *J Clin Invest*. 1995;95:2587–2593.
116. Harmsen AG, Stankiewicz M. Requirement for CD4+ cells in resistance to *Pneumocystis carinii* pneumonia in mice. *J Exp Med*. 1990;172:937–945.
119. Wiley JA, Harmsen AG. CD40 ligand is required for resolution of *Pneumocystis carinii* pneumonia in mice. *J Immunol*. 1995;155:3525–3529.
120. Beck JM, Blackmon MB, Rose CM, et al. T cell costimulatory molecule function determines susceptibility to infection with *Pneumocystis carinii* in mice. *J Immunol*. 2003;171:1969–1977.
124. Qureshi MH, Garvy BA. Neonatal T cells in an adult lung environment are competent to resolve *Pneumocystis carinii* pneumonia. *J Immunol*. 2001;166:5704–5711.
125. Phair J, Munoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med*. 1990;322:161–165.
130. Iriart X, Witkowski B, Cassaing S, et al. Alveolar and blood T lymphocyte profiles in *Pneumocystis jirovecii*-positive patients: effects of HIV status. *J Infect Dis*. 2011;204:544–553.
131. White PL, Backx M, Barnes RA. Diagnosis and management of *Pneumocystis jirovecii* infection. *Expert Rev Anti Infect Ther*. 2017;15:435–447.
142. Steele C, Marrero L, Swain S, et al. Alveolar macrophage-mediated killing of *Pneumocystis carinii* f. sp. *muris* involves molecular recognition by the dectin-1 beta-glucan receptor. *J Exp Med*. 2003;198:1677–1688.
145. Vassallo R, Kottom TJ, Standing JE, et al. Vitronectin and fibronectin function as glucan binding proteins augmenting macrophage responses to *Pneumocystis carinii*. *Am J Respir Cell Mol Biol*. 2001;25:203–211.
149. Evans HM, Simpson A, Shen S, et al. The trophic life cycle stage of the opportunistic fungal pathogen *Pneumocystis murina* hinders the ability of dendritic cells to stimulate CD4(+) T cell responses. *Infect Immun*. 2017;85.
150. Deckman JM, Kurkjian CJ, McGillis JP, et al. *Pneumocystis* infection alters the activation state of pulmonary macrophages. *Immunobiology*. 2017;222:188–197.
151. Nandakumar V, Hebrink D, Jenson P, et al. Differential macrophage polarization from *Pneumocystis* in immunocompetent and immunosuppressed hosts: potential adjunctive therapy during pneumonia. *Infect Immun*. 2017;85.
154. Inoue M, Moriwaki Y, Arikawa T, et al. Cutting edge: critical role of intracellular osteopontin in antifungal innate immune responses. *J Immunol*. 2011;186:19–23.
156. Koziel H, Eichbaum Q, Kruskal BA, et al. Reduced binding and phagocytosis of *Pneumocystis carinii* by alveolar macrophages from persons infected with HIV-1 correlates with mannose receptor downregulation. *J Clin Invest*. 1998;102:1332–1344.
161. Carmona EM, Kottom TJ, Hebrink DM, et al. Glycosphingolipids mediate *Pneumocystis* cell wall beta-glucan activation of the IL-23/IL-17 axis in human dendritic cells. *Am J Respir Cell Mol Biol*. 2012;47:50–59.
166. Paine R 3rd, Preston AM, Wilcoxen S, et al. Granulocyte-macrophage colony-stimulating factor in the innate immune response to *Pneumocystis carinii* pneumonia in mice. *J Immunol*. 2000;164:2602–2609.
168. Rudner XL, Happel KI, Young EA, et al. Interleukin-23 (IL-23)-IL-17 cytokine axis in murine *Pneumocystis carinii* infection. *Infect Immun*. 2007;75:3055–3061.
175. Travis WD, Pittaluga S, Lipschik GY, et al. Atypical pathologic manifestations of *Pneumocystis carinii* pneumonia in the acquired immune deficiency syndrome. Review of 123 lung biopsies from 76 patients with

emphasis on cysts, vascular invasion, vasculitis, and granulomas. *Am J Surg Pathol*. 1990;14:615–625.
178. Wang Z, Foye A, Chang Y, et al. Inhibition of surfactant activity by *Pneumocystis carinii* organisms and components in vitro. *Am J Physiol Lung Cell Mol Physiol*. 2005;288:L1124–L1131.
184. Atochina EN, Beck JM, Scanlon ST, et al. *Pneumocystis carinii* pneumonia alters expression and distribution of lung collectins SP-A and SP-D. *J Lab Clin Med*. 2001;137:429–439.
186. Wright TW, Gigliotti F, Finkelstein JN, et al. Immune-mediated inflammation directly impairs pulmonary function, contributing to the pathogenesis of *Pneumocystis carinii* pneumonia. *J Clin Invest*. 1999;104:1307–1317.
188. Wright TW, Notter RH, Wang Z, et al. Pulmonary inflammation disrupts surfactant function during *Pneumocystis carinii* pneumonia. *Infect Immun*. 2001;69:758–764.
193. McKinley L, Logar AJ, McAllister F, et al. Regulatory T cells dampen pulmonary inflammation and lung injury in an animal model of *Pneumocystis* pneumonia. *J Immunol*. 2006;177:6215–6226.
197. Mason GR, Hashimoto CH, Dickman PS, et al. Prognostic implications of bronchoalveolar lavage neutrophilia in patients with *Pneumocystis carinii* pneumonia and AIDS. *Am Rev Respir Dis*. 1989;139:1336–1342.
198. Benfield TL, Vestbo J, Junge J, et al. Prognostic value of interleukin-8 in AIDS-associated *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med*. 1995;151:1058–1062.
200. Benfield TL, Lundgren B, Levine SJ, et al. The major surface glycoprotein of *Pneumocystis carinii* induces release and gene expression of interleukin-8 and tumor necrosis factor alpha in monocytes. *Infect Immun*. 1997;65:4790–4794.
216. Takahashi T, Nakamura T, Iwamoto A. Reconstitution of immune responses to *Pneumocystis carinii* pneumonia in patients with HIV infection who receive highly active antiretroviral therapy. *Res Commun Mol Pathol Pharmacol*. 2002;112:59–67.
218. Sato M, Ito S, Ogura M, et al. Atypical *Pneumocystis jiroveci* pneumonia with multiple nodular granulomas after rituximab for refractory nephrotic syndrome. *Pediatr Nephrol*. 2013;28:145–149.
222. Benson CA, Spear J, Hines D, et al. Combined APACHE II score and serum lactate dehydrogenase as predictors of in-hospital mortality caused by first episode *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. *Am Rev Respir Dis*. 1991;144:319–323.
223. White PL, Posso RB, Gorton RL, et al. An evaluation of the performance of the Dynamiker(R) Fungus (1-3)-beta-D-Glucan Assay to assist in the diagnosis of *Pneumocystis* pneumonia. *Med Mycol*. 2017.
227. Huang L, Hecht FM, Stansell JD, et al. Suspected *Pneumocystis carinii* pneumonia with a negative induced sputum examination. Is early bronchoscopy useful? *Am J Respir Crit Care Med*. 1995;151:1866–1871.
229. Huang L, Stansell J, Osmond D, et al. Performance of an algorithm to detect *Pneumocystis carinii* pneumonia in symptomatic HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. *Chest*. 1999;115:1025–1032.
233. Huggett JF, Taylor MS, Kocjan G, et al. Development and evaluation of a real-time PCR assay for detection of *Pneumocystis jirovecii* DNA in bronchoalveolar lavage fluid of HIV-infected patients. *Thorax*. 2008;63:154–159.
246. Walzer PD, Evans HE, Copas AJ, et al. Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985-2006. *Clin Infect Dis*. 2008;46:625–633.
247. Fei MW, Kim EJ, Sant CA, et al. Predicting mortality from HIV-associated *Pneumocystis* pneumonia at illness presentation: an observational cohort study. *Thorax*. 2009;64:1070–1076.
249. Li MC, Lee NY, Lee CC, et al. *Pneumocystis jiroveci* pneumonia in immunocompromised patients: delayed diagnosis and poor outcomes in non-HIV-infected individuals. *J Microbiol Immunol Infect*. 2012.
252. Metersky ML, Colt HG, Olson LK, et al. AIDS-related spontaneous pneumothorax. Risk factors and treatment. *Chest*. 1995;108:946–951.
254. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed December 17, 2017.
255. Maschmeyer G, Helweg-Larsen J, Pagano L, et al. ECIL guidelines for treatment of *Pneumocystis jirovecii* pneumonia in non-HIV-infected haematology patients. *J Antimicrob Chemother*. 2016;71:2405–2413.
256. Hughes WT, Feldman S, Chaudhary SC, et al. Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of *Pneumocystis carinii* pneumonia. *J Pediatr*. 1978;92:285–291.
258. Sattler FR, Cowan R, Nielsen DM, et al. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A prospective, noncrossover study. *Ann Intern Med*. 1988;109:280–287.
262. Carr A, Swanson C, Penny R, et al. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulfamethoxazole in patients with *Pneumocystis carinii* pneumonia and AIDS. *J Infect Dis*. 1993;167:180–185.
264. Velazquez H, Perazella MA, Wright FS, et al. Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med*. 1993;119:296–301.
267. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184:992–997.
268. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med*. 1996;124:792–802.
275. Smego RA Jr, Nagar S, Maloba B, et al. A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. *Arch Intern Med*. 2001;161:1529–1533.
285. Injean P, Eells SJ, Wu H, et al. A Systematic review and meta-analysis of the data behind current recommendations for corticosteroids in non-HIV-related PCP: knowing when you are on shaky foundations. *Transplant Direct*. 2017;3:e137.
286. Wang LI, Liang H, Ye LI, et al. Adjunctive corticosteroids for the treatment of *Pneumocystis jiroveci* pneumonia in patients with HIV: a meta-analysis. *Exp Ther Med*. 2016;11:683–687.
288. Stein CR, Poole C, Kazanjian P, et al. Sulfa use, dihydropteroate synthase mutations, and *Pneumocystis jirovecii* pneumonia. *Emerg Infect Dis*. 2004;10:1760–1765.
292. Kazanjian P, Armstrong W, Hossler PA, et al. *Pneumocystis carinii* cytochrome b mutations are associated with atovaquone exposure in patients with AIDS. *J Infect Dis*. 2001;183:819–822.
294. Bhagwat SP, Wright TW, Gigliotti F. Anti-CD3 antibody decreases inflammation and improves outcome in a murine model of *Pneumocystis* pneumonia. *J Immunol*. 2010;184:497–502.
295. Kuramochi T, Hioki K, Ito M. *Pneumocystis carinii* cysts are susceptible to inactivation by chemical disinfectants. *Exp Anim*. 1997;46:241–245.