8.7.5 Pneumocystis jirovecii 1371

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8.7.5 Pneumocystis jirovecii 1371 8.7.5 Pneumocystis jirovecii Robert F. Miller and Christopher P. Eades ESSENTIALS The ascomycete fungus Pneumocystis jirovecii (previously called Pneumocystis carinii) is the cause of pneumocystis pneumonia in humans, which occurs largely among people with impaired CD4+ T-lymphocyte function or numbers (e.g. those infected with HIV, re- cipients of solid organ or haematopoietic stem cell transplants, and those taking therapeutic immunosuppressive agents). The organism is restricted to humans, and disease is now thought to arise from
de novo infection by inhalation from an exogenous source. Clinical features and diagnosis—presentation of pneumocystis pneu- monia is nonspecific, with progressive dyspnoea and nonproductive cough. Examination of the chest is typically normal, but fine bibasal end-inspiratory crackles may be heard. Diagnosis is usually by demon- stration of organisms on microscopy (preferably with immunofluor- escence staining) of induced sputum or bronchoalveolar lavage fluid. Detection of P. jirovecii-specific DNA by polymerase chain reaction is increasingly used for diagnosis. Treatment and prognosis—aside from supportive care, first-line therapy of pneumocystis pneumonia is sulphamethoxazole– trimethoprim (co-trimoxazole, which has a high rate of treatment- limiting adverse drug reactions), with adjunctive corticosteroids indicated for those with severe disease (i.e. hypoxaemia). In pa- tients whose disease is failing to respond, or those intolerant of co- trimoxazole, the main alternatives are intravenous pentamidine or clindamycin with primaquine. Among HIV-infected patients, early initiation of antiretroviral therapy (i.e. within 14 days of starting antipneumocystis pneumonia therapy) is beneficial. Prevention—primary prophylaxis is recommended for (1) HIV- infected patients—when the CD4+ count falls below 200 cells/μl or they have HIV-constitutional features or other AIDS-defining diagnoses; and (2) other at-risk groups—for example, recipients of solid organ or haem- atopoietic stem cell transplants, and those taking therapeutic immuno- suppressive agents for underlying rheumatological diseases. Secondary prophylaxis is given after an episode of pneumocystis pneumonia. The first-choice prophylactic agent is co-trimoxazole; alternative options include dapsone with pyrimethamine, and nebulized pentamidine. Introduction What is Pneumocystis jirovecii? Pneumocystis species are ascosmycetous fungi which infect a wide variety of mammalian

hosts asymptomatically but sometimes cause pneumonia, which is known as pneumocystis pneumonia (PCP). Pneumocystis jirovecii (previously called Pneumocystis carinii) is the cause of PCP in humans. Who gets PCP? Most patients have abnormalities of T-lymphocyte function or numbers but, rarely, PCP develops in patients with isolated B-cell defects and in people without evidence of immunosuppression. In non-HIV-infected people, glucocorticoid administration is an inde- pendent risk factor for development of PCP irrespective of the type or intensity of immunosuppression or the nature of the underlying disease process. In HIV-infected people, those at greatest risk of PCP have CD4+ T-lymphocyte counts less than 200 cells/μl. In the early years of the AIDS epidemic, PCP was the AIDS-defining diagnosis for almost two-thirds of patients. Since the introduction of antiretro- viral therapy (ART), although there has been a marked decline in incidence of PCP, it remains the most common serious opportun- istic infection in HIV-infected people in Europe, the United States of America, and Australasia. Patients living in areas without access to PCP prophylaxis or ART remain at high risk of PCP. Aetiology Pneumocystis cannot reliably be cultured in vitro. Pneumocystis or- ganisms from different mammalian host species show antigenic, karyotypic, and genetic heterogeneity. Cross-infection between host species has not been successful, suggesting host specificity and that pneumocystis infection in humans is not a zoonosis. The demonstration of antibodies against pneumocystis in most healthy children and adults has been regarded previously as supportive of the hypothesis that PCP arises in an immunocompromised indi- vidual by reactivation of a childhood-acquired latent infection. However, this hypothesis is challenged by the failure to demonstrate pneumocystis in bronchoscopic alveolar lavage fluid or necropsy lung tissue of immune competent people and the observation that Pneumocystis DNA is detectable only at low levels in less than 25% of HIV-infected people with low CD4+ T-lymphocyte counts pre- senting with respiratory episodes and with diagnoses other than PCP. Human Pneumocystis infection is currently thought to arise from de novo infection from an exogenous source. Finding different genotypes in each episode in patients with recurrent PCP supports the reinfection model. Pathogenesis After inhalation, the organism reaches the alveoli where the trophic form attaches to type 1 pneumocytes. In an immune competent person, the organism is eliminated; in the immunodeficient, PCP will develop. The major surface glycoprotein of Pneumocystis binds to macro- phages and induces T-lymphocyte proliferation and increased se- cretion of L1 (L1CAM, CD171), L2 and tumour necrosis factor-α (TNFα). Monocytes respond to major surface glycoprotein by re- leasing interleukin-8 and TNFα. Pneumocystis induces changes in the quantity and quality of pulmonary surfactant; total cholesterol, glycerol, and phospholipase A2 are increased while phospholipid is reduced. Clinical presentation Patients typically present with progressive exertional dyspnoea, a nonproductive cough, and fever of several days or weeks duration.

 They often report an inability to take in a deep breath that is not due to pleural pain. Purulent sputum, haemoptysis, and pleural pain are atypical for PCP and suggest a bacterial or mycobac- terial pathogen. In HIV-infected patients, the presentation is usu- ally more indolent than in patients immunosuppressed for other reasons. However, in a small proportion of HIV-infected patients, the disease course of PCP is fulminant with an interval of 7 days or fewer between onset of symptoms and progression to respira- tory failure. Rarely, PCP might present as pyrexia of undetermined origin. Examination of the chest is usually normal; occasionally, fine bibasal end-inspiratory crackles are heard. Signs of focal consolida- tion or pleural effusion suggest an alternative diagnosis. Pathology Within the lung, Pneumocystis infection is characterized by an eo- sinophilic, foamy intra-alveolar exudate, associated with a mild plasma-cell

interstitial pneumonitis. Morphologically, two forms of Pneumocystis can be identified: thick-walled cystic forms (6–7 μm diameter) that lie freely within the alveolar exudate are demon- strated by Grocott-Gömöri methenamine silver, toluidine blue O, or cresyl violet stains (Fig. 8.7.5.1). The exudate consists largely of thin-walled, irregularly shaped, single-nucleated trophic forms (2–5 μm diameter) that are shown by Giemsa stain but lack dis- tinctive features. Uncommonly, interstitial fibrosis, diffuse alveolar damage, granulomatous inflammation, nodular and cavitary lesions, and pneumatocele formation may occur. Before the availability of ART Pneumocystis infection extending beyond the airspaces; extrapulmonary pneumocystosis involving liver, spleen, gut, or eye was reported and was strongly associated with use of nebulized pentamidine for prophylaxis. Investigations Chest radiograph The chest radiograph can be normal in early or mild PCP. With more severe disease or later presentation, bilateral perihilar inter- stitial or reticular infiltrates are seen (Fig. 8.7.5.2). These might progress to diffuse bilateral alveolar (air space) consolidation that mimics pulmonary oedema. In the late stages, the lungs can be massively consolidated and almost airless. Radiographic de- terioration from near normal at presentation to being markedly abnormal might occur over 48 h or less. Up to 20% of chest radio- graphs are atypical, showing intrapulmonary nodules, cavitary le- sions, lobar consolidation, pneumatoceles (Fig. 8.7.5.3), or hilar/ mediastinal lymphadenopathy. All of these typical and atypical radiographic appearances can also be seen in bacterial, mycobac- terial, and fungal infections and in nonspecific pneumonitis and pulmonary Kaposi sarcoma. Despite treatment and clinical recovery, in some individuals the chest radiograph might remain abnormal for many months in the absence of symptoms. In others, postinfectious bronchiectasis or fi- brosis develops. Arterial blood gases/oximetry Less than 10% of patients with PCP have a normal partial pressure of oxygen (PaO_2) and a normal Alveolar-arterial gradient ($P(A–a)O_2$). These measures are sensitive, though not specific, for PCP as they Fig. 8.7.5.1 Cystic form of Pneumocystis jirovecii in bronchoalveolar lavage fluid. The walls of the cysts are stained black (Grocott-Gömöri methanamine silver stain). Fig. 8.7.5.2 Chest radiograph showing bilateral interstitial infiltrates typical of Pneumocystis pneumonia.

 can also occur in bacterial pneumonia, pulmonary Kaposi sarcoma, and tuberculosis. CT High-resolution CT of the chest might be useful in the symptom- atic patient with a normal or equivocal chest radiograph. Areas of ‘ground-glass’ shadowing indicate active pulmonary disease (Fig. 8.7.5.4). Subpleural sparing is a common radiological feature. Such appearances can be caused by other fungal infections and by cytomegalovirus, as well as by PCP. Alveolar haemorrhage might also be a relevant differential in haematopoietic stem cell transplant recipients. Induced sputum Spontaneously expectorated sputum is inadequate for diagnosis of PCP. Sputum induction by inhalation of ultrasonically nebu- lized hypertonic (3–5%; 513–856 mmol/litre) saline might provoke a suitable sample. Pneumocystis is usually found in clear saliva- like samples. Purulent samples suggest an alternative diagnosis. The sensitivity varies between 55 and 90% and a negative result for Pneumocystis should prompt further diagnostic tests. Induced sputum might have a higher yield for PCP diagnosis in HIV-infected patients, in whom sputum organism-load is higher than in those with immunosuppression of alternate aetiology. Bronchoscopy Fibre-optic bronchoscopy with bronchoalveolar lavage has a sensitivity exceeding 90% for detection of Pneumocystis. Immunofluorescence (IF) staining increases the diagnostic yield compared to conventional histochemical staining. Transbronchial biopsies add very little to the diagnostic yield and are associated with a relatively high complication rate (c.8%). As Pneumocystis persists in the lung for many days (and even weeks) after the start of antimicrobial therapy, bronchoscopy can be performed up to 1 week after commencing antimicrobial therapy without a reduc- tion in

diagnostic yield. Molecular detection tests Detection of Pneumocystis-specific DNA by the polymerase chain reaction (PCR) on bronchoalveolar lavage fluid and induced sputum is superior to conventional histochemical methods and offers sen- sitivity approaching 100%. However, specificity is reduced, as Pneumocystis-specific DNA can also be detected in immunosup- pressed patients who are colonized with P. jirovecii, and who have alternative explanations for their presentation (e.g. bacterial pneu- monia). PCR might, therefore, be of most diagnostic benefit for the patient with a high pretest probability of PCP and negative results from histochemical staining and IF of bronchoalveolar lavage fluid or induced sputum. Detection of Pneumocystis DNA by PCR might also be achieved on oropharyngeal samples obtained by gargling with 10 ml normal saline. Empirical therapy Many centres in the United Kingdom and North America seek to confirm a diagnosis in every suspected case of PCP. Others treat HIV-infected patients empirically when they present with fea- tures typical of PCP: symptoms and signs, chest radiographic ab- normalities, and hypoxaemia. Bronchoscopy is reserved for those who fail to respond to empirical therapy by day 5 or who have atypical presentations. Both strategies are equally effective in clin- ical practice. Treatment It is important to stratify PCP as mild (PaO2 on air >11.0 kPa, SaO2

> 96%), moderate (PaO2 8.0–11.0 kPa, SaO2 91–96%), or severe Fig. 8.7.5.3 Chest radiograph showing atypical appearances for Pneumocystis pneumonia, including bilateral apical shadowing and a right mid-zone thin-walled pneumatocele. Fig. 8.7.5.4 CT of thorax showing diffuse bilateral ‘ground-glass’ shadowing typical of Pneumocystis pneumonia.

section 8 Infectious diseases 1374 (PaO2 <8.0 kPa, SaO2 <91%) as some drugs are unproven or inef- fective in severe disease. First-choice treatment is high-dose co-trimoxazole (sulphameth- oxazole 100 mg/kg per day and trimethoprim 20 mg/kg per day, in two to four divided doses orally or intravenously). In HIV-infected patients with PCP, 21 days are recommended; in those with other causes of immunosuppression, between 14 and 21 days are frequently given. In mild disease, oral medication may be given throughout; in moderate or severe disease, intravenous therapy is usually given for the first 7 to 10 days, then orally. Another treatment in patients with severe disease is clindamycin (450–600 mg three to four times daily orally or intravenously) with primaquine (15–30 mg once daily orally). Despite its toxicity, pentamidine (4 mg/kg per day intravenously) can be used if other treatments have failed. In patients with mild or moderate disease, alternatives to co-trimoxazole include clindamycin with prima- quine (doses as described here), dapsone (100 mg once daily or- ally) with trimethoprim (20 mg/kg per day orally), or atovaquone (750 mg twice daily orally). Nebulized pentamidine has no role in treatment of PCP; treatment response is delayed, early relapse is common, and extrapulmonary dissemination of pneumocystosis is not suppressed. Current US and UK Guidelines recommend that HIV-infected patients presenting with PCP should commence ART within 14 days after starting anti-PCP therapy. There is a risk of immune reconsti- tution inflammatory syndrome; patients experiencing paradoxical worsening of symptoms, oxygenation, and radiographic appearances. Adjuvant steroids HIV-infected patients with moderate or severe PCP and PaO2 less than 9.3 kPa (on air) benefit from adjuvant corticosteroids, which might reduce the need for mechanical ventilation and risk of death. Many non-HIV-infected patients with PCP are already receiving glucocorticoids as part of their regimen of immuno- suppression and the benefits of dose increases have not clearly been demonstrated. Adjunctive glucocorticoid regimens include prednisolone (40 mg twice daily orally

for 5 days, then 40 mg once daily on days 6 to 10, then 20 mg once daily on days 11 to 21) or methylprednisolone (intravenously at 75% of these doses). The benefit of adjuvant corticosteroids has only been documented when they are started within 72 h of starting specific anti-PCP therapy. Adverse reactions Adverse reactions to co-trimoxazole, which usually occur between days 6 and 14 of treatment, are more common in HIV-infected pa- tients than in patients with other causes of immunosuppression. Anaemia and neutropenia (≤40% of patients), rash and fever (≤30% each), and biochemical hepatitis (≤15%) are the most frequent ad- verse reactions. Coadministration of folic or folinic acid does not at- tenuate haematological toxicity. Diarrhoea and rash (≤30% each) are the most frequent adverse reactions to clindamycin. Stool should be examined for Clostridium difficile in patients developing diarrhoea on clindamycin. Glucose-6-phosphate dehydrogenase deficiency Glucose-6-phosphate dehydrogenase levels should be checked before (or as soon as possible after) starting treatment with co-trimoxazole, dapsone, or primaquine, but treatment initiation should not be de- layed pending the result. If haemolysis occurs, or enzyme deficiency is identified, alternative treatment can be started (e.g. intravenous pentamidine or atovaquone). Prophylaxis HIV-infected patients are at increased risk of PCP as the CD4+ T- lymphocyte count decreases. Primary prophylaxis (to prevent a first episode of Pneumocystis pneumonia) is given when the CD4 count falls below 200 cells/µl or the CD4:total lymphocyte ratio is less than 1:5, to patients with HIV-constitutional features (unexplained fever of three or more week’s duration or oral candida irrespective of CD4 count), and to patients with other AIDS-defining diagnoses, for ex- ample, Kaposi sarcoma. Secondary prophylaxis is given after an epi- sode of PCP. The first-choice agent for primary and secondary prophylaxis is co- trimoxazole (960 mg daily: 800 mg sulphamethoxazole and 160 mg trimethoprim). A lower dose (i.e. 960 mg three times weekly or 480 mg daily) might be equally effective and have fewer side effects. Co-trimoxazole may also protect against bacterial infections and re- activation of cerebral toxoplasmosis. Alternative, less effective options include nebulized pentamidine (300 mg once monthly, or once per fortnight if the CD4 count is 50 µl or less), dapsone (100 mg daily) with pyrimethamine (25 mg once weekly (and folinic acid)), atovaquone (750 mg twice daily), and azithromycin (1.25 g once weekly). Non-HIV-infected patients with high attack rates of PCP should receive prophylaxis (drug choice and doses as described here). At- risk groups include those with acute leukaemias, severe combined immunodeficiency syndrome, Hodgkin lymphoma, rhabdomyo- sarcoma, primary and secondary central nervous system tumours, granulomatosis with polyangitis, and organ transplantation including allogenic haematopoietic stem cell, renal, heart, heart/lung, and liver. Infection control considerations The mode of transmission of human Pneumocystis infection is un- clear but recent molecular data suggest that transmission might occur from infected patients to susceptible immunocompromised individuals. Patients with minor immune suppression, including those with moderate to severe chronic obstructive lung disease, and those receiving long-term corticosteroids (prednisolone 20 mg/day or more), irrespective of the cause of underlying immune suppres- sion, might be colonized by Pneumocystis, thus acting as a poten- tial infectious reservoir. Nosocomial outbreaks have been described in cohorts of both HIV-infected and non-HIV-infected patients. Pneumocystis DNA can be isolated from air in the environs of pa- tients with PCP. Where available, respiratory isolation might be prudent, particularly on inpatient units responsible for care of im- munocompromised patients. Areas of uncertainty/future research The drug target for sulphamethoxazole and dapsone is dihydropteroate synthase (DHPS). Mutations in the DHPS gene of Pneumocystis occur

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