Journal Club

SK Yung

Pneumocystis Pneumonia

Historical Background

- First identified by Chagas in 1909
  - ? A new trypanosomal life form
- Carini in 1910
  - Similar findings and thinking
- Delanoe in 1912
  - A separate species from *Trypanosoma*
  - *Pneumocystis carinii*

Historical Background

- Before World War II
  - Epidemic form of interstitial plasma cell pneumonitis of unknown etiology in malnourish infants
- In 1951 and 1952, Vanek and Jirovec
  - Association of *Pneumocystis* in the lung among premature and malnourished children with interstitial plasma cell pneumonitis in nursing homes

Historical Background

- In 1960s
  - An opportunistic pathogen in children with acute leukemia/ congenital immunodeficiency impairing T-lymphocyte function
- In 1981
  - First opportunistic infection in homosexual men in the US with 'Gay's syndrome' (AIDS)

Taxonomy

- Initially thought = a protozoan
  - Morphology
  - Response to antiprotozoan drug like pentamidine
- Now classified as a fungus
  - Genetic analysis of ribosomal RNA
  - Cell wall resemble other fungi (beta-1,3-glucan)

Taxonomy

- Atypical fungal micro-organisms
  - Unable to grow in vitro in fungal culture media
  - Respond to antiparasitic agents
  - Cell wall contains cholesterol rather than ergosterol (Polyenes = inactive)

Taxonomy

- Pneumocystis = a genus with numerous species
  - DNA analyses, host species specificity
- *Pneumocystis jirovecii*
  - The form that infects humans
- *Pneumocystis carinii*
  - 1 of 2 species that infects rats
- A focus of continuing controversy

Microbiology and Pathogenesis

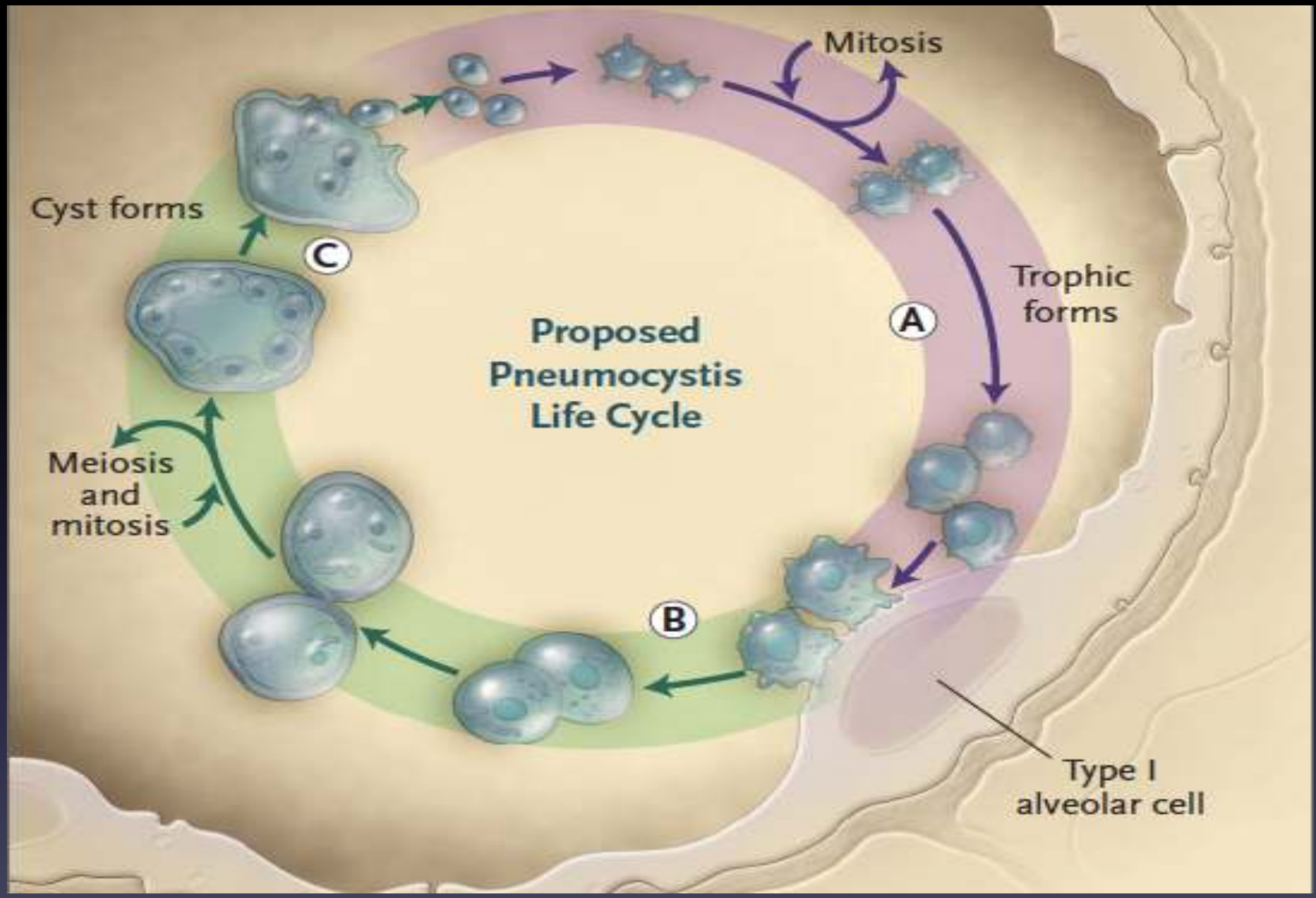
- Life cycle not fully understood
- Unable to cultivate in vitro
- Studies based mainly on light and electron microscopic analysis

Microbiology and Pathogenesis

- Two predominant life forms
  - Trophic form (1-4µm in diameter)
  - Cyst form (8-10µm in diameter)
- Three intermediate cyst stages
  - Early, intermediate, late precysts
- ? Trophic forms conjugate to form cysts and undergo maturation, produce trophic forms as it ruptures

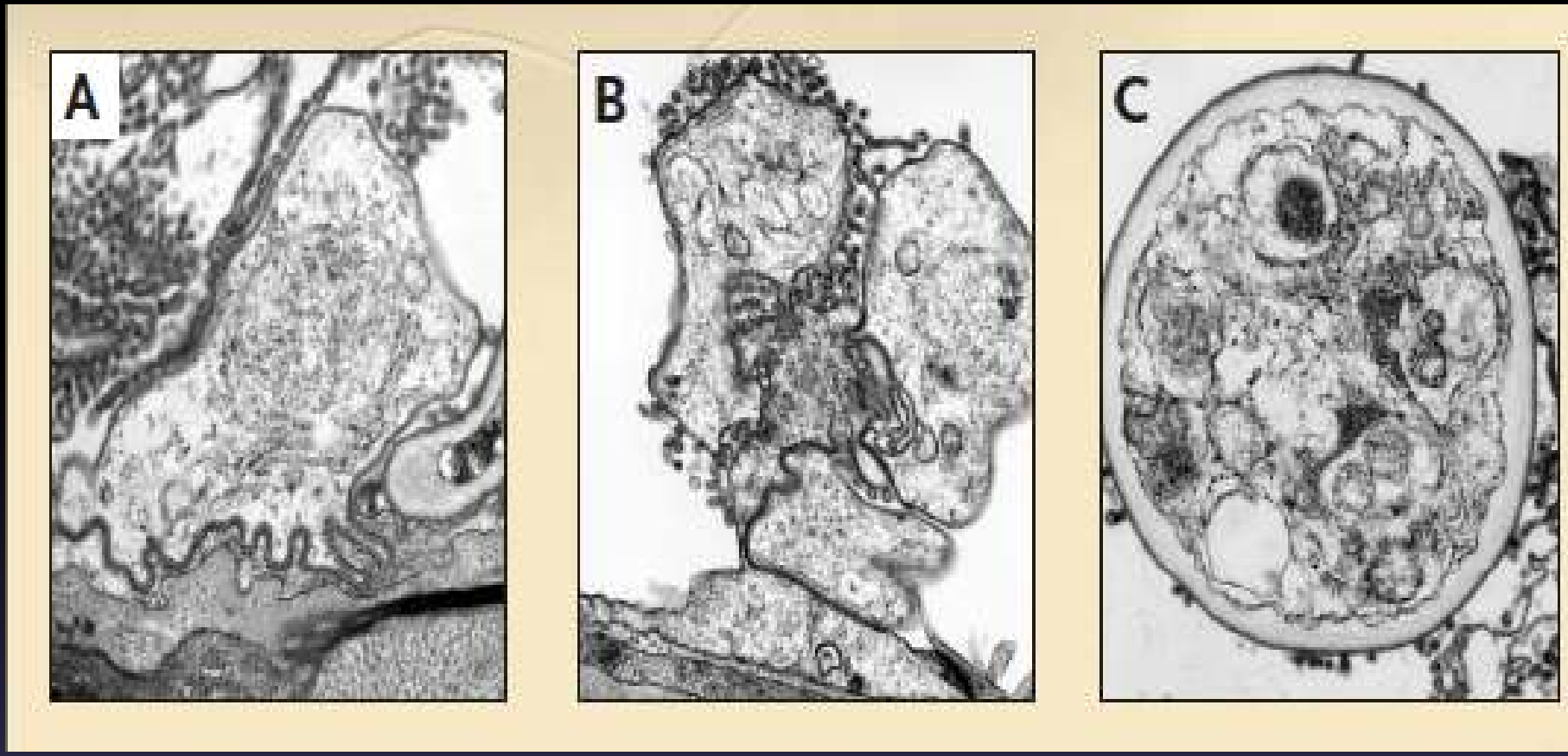
Microbiology and Pathogenesis

- Trophozoite attaches to the alveolar type I cells, obtains nutrients from the alveolar fluid / cells and proliferates
- Adherence alone does not disrupt the structure or barrier function of alveolar epithelial cells
- Rather, inflammatory responses in the host with changes in surfactant proteins are primarily responsible for the compromise of the alveolar-capillary surface



Proposed pneumocystis lifecycle

NEJM 2004;350: 2487-98



A: Trophic form attaching the alveolar epithelium
B: Trophic forms attaching to one another
C: Cyst form

Proposed pneumocystis lifecycle

NEJM 2004;350: 2487-98

Microbiology and Pathogenesis

- Key components of host immune response
  - Lymphocytes esp. CD_4+ T cells
    - Association of CD_4+ count and PCP in HIV +ve patients
  - Macrophages
    - Principal phagocytes mediating the uptake and degradation of the organisms in the lung
  - Cytokines and chemokine e.g. TNFα, IL-8

Microbiology and Pathogenesis

- Effective inflammatory responses are required to control pneumocystis pneumonia
- However, exuberant inflammation also promotes pulmonary injury
- Respiratory impairment and death are more closely correlated with the degree of lung inflammation than with the organism burden

Epidemiology - Transmission

- Route of transmission remains uncertain
- Serological studies have shown that many infants have been infected by P. jerovecii. Reactivation from a latent infection has been popular for decades
- However, latest epidemiologic and experimental evidences support human to human transmission

Epidemiology - Transmission

- Evidence for human to human transmission
  - Geographic clustering of cases of PCP and genotypes found in the patients are similar to those found in the current patient's environment but not those from his/her place of birth
  - Several nosocomial outbreaks have been reported
    - Molecular typing showed that one strain is predominant

Epidemiology - Transmission

- ? Route. (direct contact / droplet/ airborne)
- Airborne transmission has received the most attention
  - Demonstrated in animal models
  - Detected in air samples from patient's surroundings (as far as 8 meters away)
  - Some cases are in different rooms during nosocomial outbreaks
- Vertical transmission has also been proposed (found in both the placental and fetal lung tissues of aborted cases

? Need of airborne/Single room isolation

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports April 10, 2009 / Vol. 58 / No. RR-4

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

Preventing Exposure

Certain authorities might recommend that persons who are at risk for PCP not share a hospital room with a patient who has PCP, a recommendations based on animal studies and anecdotal human experience. Data are insufficient to support this recommendation as standard practice (CIII).

? Need of airborne/Single room isolation

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Recommendations and Reports | September 4, 2009 / Vol. 58 / No. RR-11

Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics

Preventing Exposure

The need for isolation of hospitalized persons who have PCP has been neither demonstrated nor discounted. PCP patients clearly do not need to be isolated from persons with normal immune responses and from immunocompromised high-risk patients who are receiving PCP prophylaxis. Under unusual circumstances where prophylaxis cannot be administered, avoid placement in the same room with an immucompromised patient (CIII).

Epidemiology - Colonization

- PCP seems to succeed to a dynamic process of infection, the role of colonization should be of major importance in transmission
- A permanent colonization/ clearance cycle has been demonstrated in humans
- Prevalance of colonization among healthy adults is low, 0-20%
  - N.B. Different techniques/samples used

Epidemiology - Colonization

- Groups at higher risk of colonization
  - HIV (31 - 68%)
  - Chronic lung disease esp. COAD (37-55%)
    - Frequency of colonization correlated with more severe stages of COPD, ? Role in progression of disease
  - Smoker
  - DM, Multiple myeloma, CLL, Sarcoidosis, Corticosteroid treatment …

Groups at risk for PCP

- HIV +ve
  - Risk increases with lower CD_4 count and develops predominantly in those < 200 cells/µL
  - Most HIV +ve who develop PCP are unaware of their HIV infection or are outside of medical care

Groups at risk for PCP

- Non HIV immunocompromised hosts
  - Routine use of PCP prophylaxis and HAART in HIV infected patients -> patients without HIV account now for the majority of cases of PCP in industrialized countries
  - No biological quantitative marker clearly correlated with the risk of Pneumocystis infection in these patients as CD_4 count in HIV infection

Non HIV immunocompromised hosts

- Haematological malignancies
  - The most common underlying immunosuppressive conditions
  - ALL patients were historically at higher risk but condition changed with the routine use of PCP prophylaxis
  - Some specific therapeutic regimes are particularly associated
    - Corticosteroid, purine analogues e.g. fludarabine, vincristine, cyclophosphamide, monoclonal antibody therapies e.g. alemtuzumab (antiCD52), rituximab (antiCD20)

Non HIV immunocompromised hosts

- Solid tumour
  - Steroid use seems to be the common predisposition
    - 50% patients with solid tumour at diagnosis of PCP had primary or metastatic brain tumours and had received high doses of corticosteroids
  - Most of the cases of PCP in patients without brain lesions are patients with lung or breast neoplasm
    - ? Related to smoking / thoracic irradiation

Non HIV immunocompromised hosts

- Inflammatory and Collagen Vascular disease
  - Overall incidence <= 2%
  - Patients with Wegener Granulomatosis are at higher risk in particular, most occurred during the tapering of steroid
  - SLE, dermatomyositis/ polymyositis etc

Non HIV immunocompromised hosts

- Solid organ transplantation
  - Attack rate highest in recipients of lung/heart lung transplants
  - Usually occurs in the first 6 months of post transplant period
  - Practices in immunosuppresive therapy continually change and may modulate the risk of infection e.g. increasing use of monoclonal antibodies would probably increase the risk

Non HIV immunocompromised hosts

- Bone marrow and haematopoietic stem cell transplantation
  - Severe and prolonged immunosuppression makes them vulnerable to PCP
  - Prophylaxis with Septrin is effective and most cases that developed PCP did not receive adequate prophylaxis

Non HIV immunocompromised hosts

- Miscellaneous conditions
  - Idiopathic CD_4 lymphocytopenia, GOOD syndrome…
  - Cushing Syndrome

Clinical presentation – HIV +ve

- Subtle onset of progressive dyspnoea, non productive cough, low grade fever
- Acute dyspnoea with pleuritic chest pain may indicate the development of pneumothorax
- Physical examination
  - Tachypnoea, tachycardia and normal findings on auscultation

Clinical presentation – HIV +ve

- Significantly increased number of pneumocystis organisms in the lungs, with fewer neutrophils than do patients with PCP without AIDS
- Higher diagnostic yield of induced sputum and BAL
- Better oxygenation and survival (mortality rate 10-20% but increases substantially with the need of mechanical ventilation

Clinical presentation – HIV -ve

- Abrupt onset of respiratory insufficiency that may correlate with a tapered or increased dosage of immunosuppressant medications
- More neutrophils and fewer organisms in the lungs during an episode of PCP
  - Mortality 30-60%, cancer > transplantation > CTD

Radiographic features - CXR

- Typically bilateral perihilar interstitial infiltrates that become increasing homogeneous and diffuse as the disease progress
- Normal at diagnosis of PCP in as many as 39%
- HRCT is more sensitive

Radiologic features - HRCT

- Ground-glass opacities with patchy distribution, predominating in perihilar regions of lungs
- Thickened septal lines, consolidations may be present
- Multiple cysts (10-34%, increases risk of pneumothorax)
- Atypical manifestations
  - Multiple thick walled cavitary nodules and noncavitary nodules
  - LNs and effusions : less frequent
  - Note: Cases receiving aerosolizied pentamidine prophylaxis are more likely to present with with predominantly upper lobe disease, pneumothorax or cyst

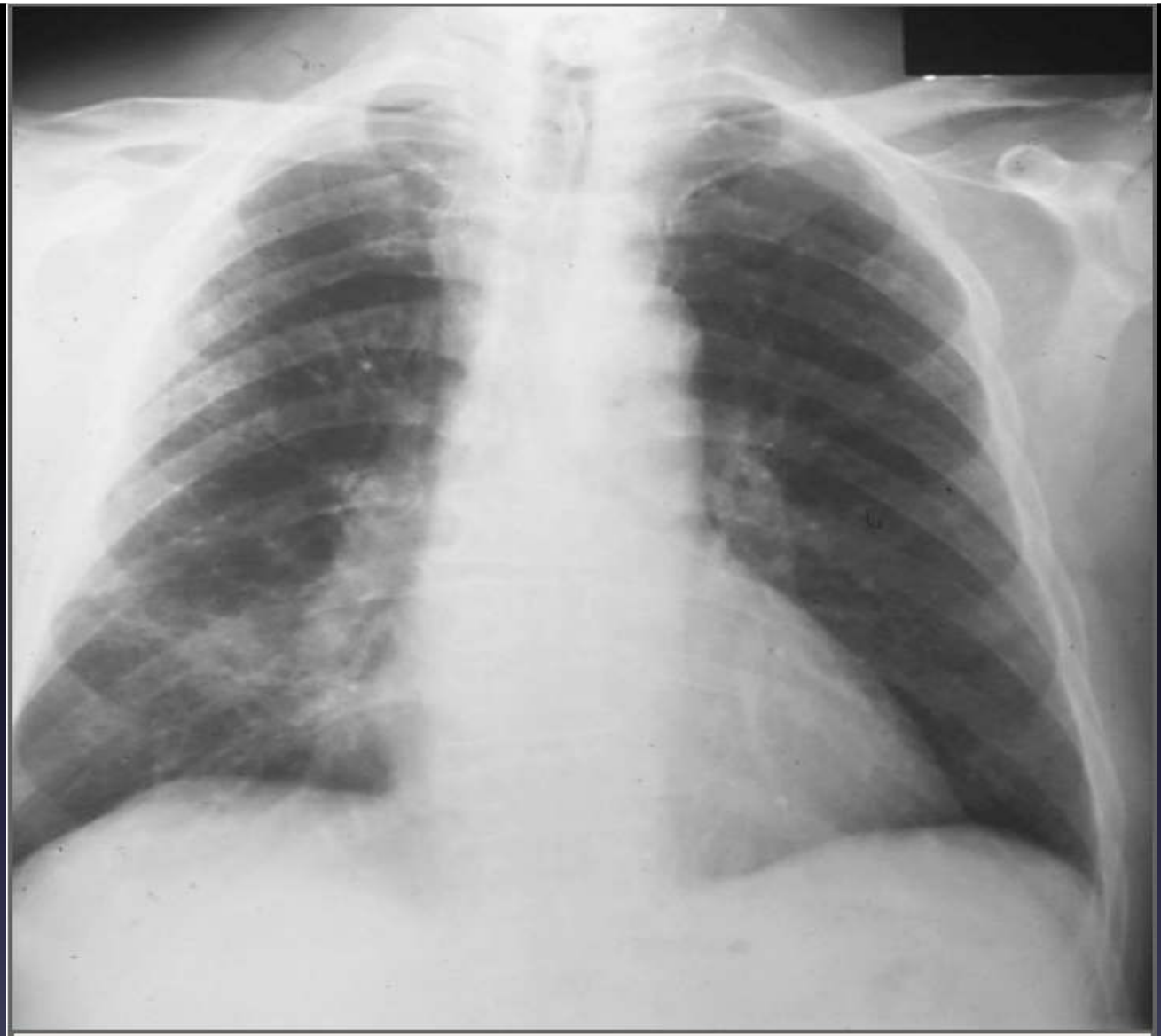

Figure 1. Posteroanterior Chest Radiograph of a 68-Year-Old Patient with Pneumocystis Pneumonia That Developed as a Consequence of Long-Term Corticosteroid Therapy for an Inflammatory Neuropathy.

Mixed alveolar and interstitial infiltrates are more prominent on the right side than on the left.

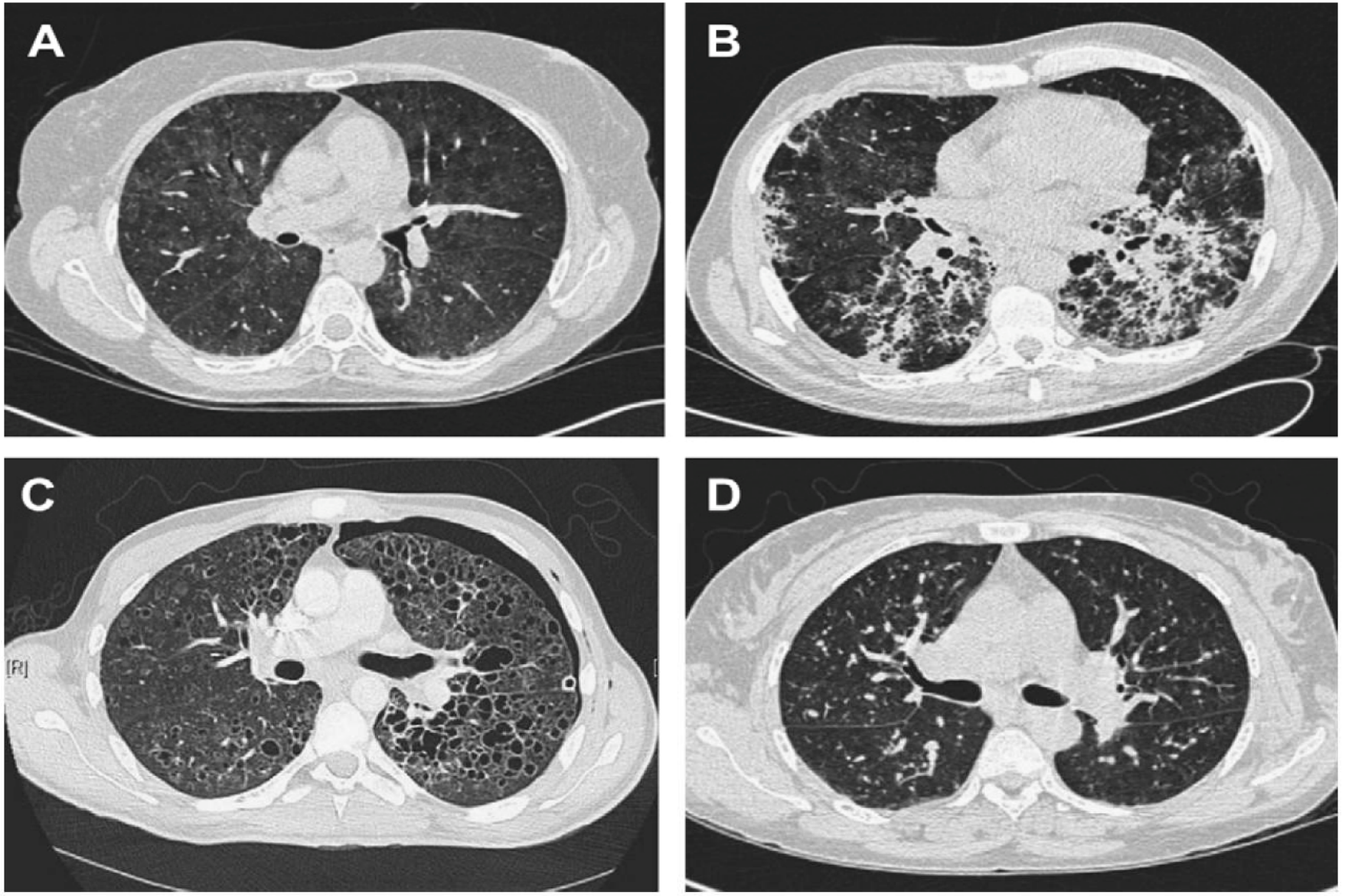

Fig. 1. *Pneumocystis* pneumonia appearances on high-resolution CT scan. (*A*) Diffuse ground-glass opacities. (*B*) Thickened septal lines and areas of consolidation. (*C*) Diffuse ground-glass opacities and multiple cysts. Left pneumothorax and chest-tube. (*D*) Multiple nodules in a granulomatous *Pneumocystis* pneumonia.

Microbiological diagnosis

- Pneumocystis cannot be readily cultured in the laboratory, diagnosis rely on the microscopic demonstration of the organism in respiratory specimen

Detection/Staining method

- Trophic forms by e.g. Giemsa
- Cysts by e.g. Gomori-methenamine silver
- Fluorescein – labeled monoclonal antibodies
  - Detect both trophic forms and cysts
  - More sensitive than general stains, = 'gold standard'

Detection/Staining method

- PCR
  - Conventional
    - High sensitivity but low specificity, main use = high negative predictive value -> withdrawal of antiPCP
  - Quantitative
    - More promising, as a cut off of clinical significance maybe determined for differentiation between carriage and PCP
  - Note: most studies used home made PCR, precluding generalization of results. PCR is still a clinical research tool

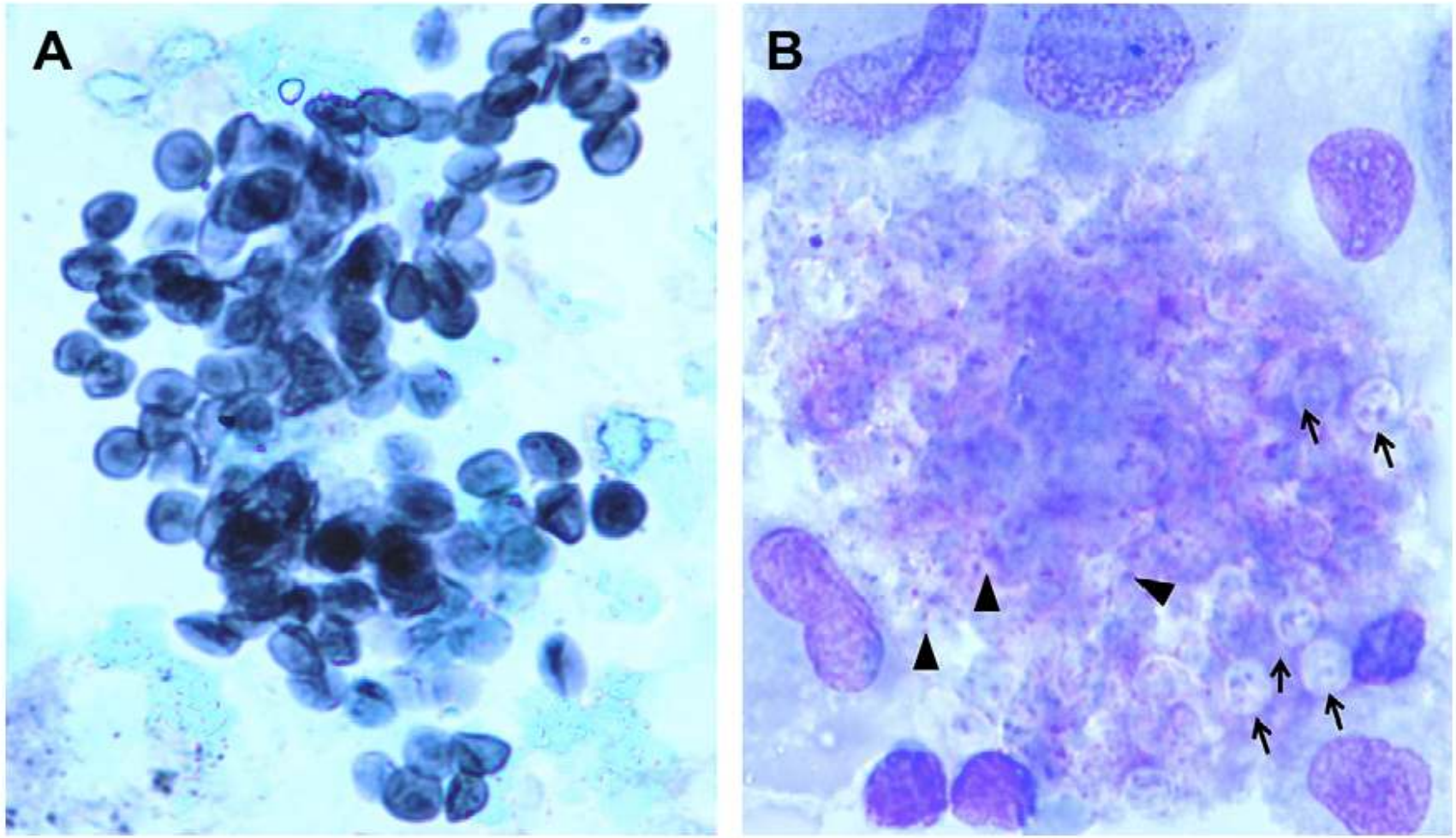

Fig. 2. Typical *Pneumocystis* forms in a bronchoalveolar lavage specimen stained with Gomori methamine silver (*A*) and Giemsa (*B*) (original magnification × 500). (*A*) Gomori methamine silver stains the cyst walls. Cysts are well recognizable as round, oval, or flat bodies of approximately 4–5 μm in diameter. (*B*) Giemsa staining showing trophic forms and cysts of *Pneumocystis jirovecii* within foamy exudates. Cyst structures containing intracystic bodies at their periphery (*arrows*); trophic forms are visible with dotlike nuclei and pale blue-gray cytoplasm (*arrowheads*).

What specimen?

- Induced sputum (with hypertonic saline)
  - Rapid and cost effective
  - Sensitivity 55-66% in HIV infected patients with conventional staining. > 90% with monoclonal antibodies
- Bronchoscopic lavage
  - PCP patients without AIDS / HIV infected patient with early disease/ Breakthrough episodes while receiving aerosol pentamidine prophylaxis have a lower burden of P. jerovecii
  - Preferred diagnostic procedure (reported sensitivity 89 – 98%)
- N.B. Granulomatous Pneumocystis, an atypical form of PCP, BAL is usually –ve and requires open lung biopsy

Treatment - Agent

- Trimethroprim-sulfamethoxazole (Septrin) = 1st line agent for mild to severe PCP either in HIV and Non HIV infected patients
  - High efficacy and the availability of oral and parental forms
  - Adverse effects usually begin during the 2nd week of treatment. More common in HIV infected patients

Treatment - Agent

- Parental Pentamidine
  - The most studied drug as an alternative to TMP-SMX
  - About as effective as TMP-SMX
  - Principal limitation = poor tolerability
    - Adverse reactions in 71%, leading to drug withdrawal in 18%. (Nephropathy, hyperkalemia, dysglycemia, hepatotoxicity, pancreatitis..)

Treatment - Agent

- No clinical trials to compare atovaquone, clindamycin-primaquine or dapsone-TMP with TMP-SMX in treatment of moderate to severe PCP (PaO_2 < 70mmHg / A-a gradient > 35mmHg)
- More data in mild to moderate PCP (A-a gradient > 35mmHg and 35-45mmHg)
  - Clindamycin-primaquine and dapsone-TMP comparable efficacy and toxicity to TMP-SMX
  - Atovaquone less effective but better tolerated than TMP-SMX

?? Role of echinocandins

- Experience is limited
- 2 case reports (2 patients) treated successfully with caspofungin alone
- 4 patients (solid organ transplant) received caspofungin in addition to TMP-SMX (2 as salvage treatment) with rapid improvement
- However another case report with 2 patients received conventional PCP treatment and concomitant use of echinocandins for presumed invasive aspergillus. In both cases, PCP progressed, and patient died.

? Gene mutations/ treatment failure

- No clear association between mutations in the dihydropteroate synthetase (DHPS), the target enzyme of sulfonamides, and TMP-SMX treatment failure or altered outcome has been demonstrated

Table 1
Treatment of *Pneumocystis* pneumonia

	Medication	Dose and Route	Comments	Adverse Events
First choice	Trimethoprim + sulfamethoxazole	15–20 mg/kg 75–100 mg/kg Intravenous or orally, divided into 3–4 doses daily	Contraindication in cases of allergy to sulfa drugs	Cytopenia Skin reactions (mild to severe: toxic epidermal necrolysis, Stevens-Johnson syndrome) Hepatitis, pancreatitis Gastrointestinal disturbance Renal insufficiency, hyperkalemia Anaphylaxis
Alternative choice Mild to moderate PCP	Dapsone + trimethoprime	100 mg/d orally 5 mg/kg 3 times daily	Contraindication in cases of G6PD deficiency Possible cross-reaction with sulfa allergy	Methemoglobinemia Skin rash Fever Gastrointestinal disturbance
	Atovaquone	750 mg 2–3 times daily orally	Bioavailability increased with high-fat meal	Skin rash Fever Gastrointestinal disturbance Hepatitis
	Clindamycin + primaquine	600 mg 4 times daily intravenous or 350–400 mg 4 times daily orally 30 mg daily orally	Contraindication in cases of G6PD	Skin rash Fever Neutropenia Gastrointestinal disturbance Methemoglobinemia
Alternative choice Moderate to severe PCP	Pentamidine	4 mg/kg daily intravenous		Hypotension, Cardiac arrhythmias (torsades de pointes) Hyperkalemia, hypomagnesemia, hypocalcemia Renal insufficiency Pancreatitis, hypoglycemia (early), diabetes mellitus (late) Neutropenia Hepatitis

When to declare treatment failure ?

- Pre-corticosteroid era, generally improved after 4-8 days.
- Progression after 4 days -> 2nd pathogen should be excluded and another treatment of PCP considered.

Duration of treatment

- HIV infected : 21 days
- Non HIV immunocompromised : 14 days
- Longer treatment in HIV infected patients due to a higher organism burden and a slower clinical response -> higher risk of relapse after 14 days of treatment
- Treatment should be prolonged in non HIV infected patients when clinical improvement in prolonged

Corticosteroids in HIV infected patients

- Inflammation correlated to lung injury in animal models
- Randomized trials evaluated the efficacy of corticosteroid
  - In those PaO2 <= 70mmHg or A-a gradient 35mmHg or more
  - Reduce mortality and morbidity
  - Benefit begins during the 1st 72 hours of treatment
  - Regime e.g. Prednisolone 40mg BD x 5 days, 40mg daily x 5 days, 20mg daily x 11 days

Corticosteroid in Non-HIV infected patients

- No randomized studies
- Heterogeneous group of patients and most have corticosteroid at the time they developed PCP
- Mixed results for retrospective studies
- Routine use of adjunctive corticosteroid could NOT be recommended
- *Tapering of steroid should be avoided, and whether doses should be increased must be individualized*

The unmasking of *Pneumocystis jiroveci* pneumonia during reversal of immunosuppression: case reports and literature review

Alan KL Wu[1], Vincent CC Cheng[1], Bone SF Tang[1], Ivan FN Hung[1], Rodney A Lee[1], David S Hui[2] and Kwok Y Yuen*[1]

BMC Infectious Diseases 2004, 4:57

Table 1: Summary of literature reported cases of HIV-negative immunocompromised patients with PCP manifested as IRD

Case [Ref.]	Sex/Age (years)	Underlying disease (s)	Reduction of IS level before symptoms onset of IRD	Symptoms & signs at IRD; change of lymphocyte count before & during IRD (if mentioned)	Treatment, clinical progress & outcome
1–7 [22]	M/F: 4:3 Median age 12, range 2–25	Acute leukemia in remission (4), acute leukemia in relapse (1), Hodgkin's disease (1), embryonal carcinoma of testes (1)	P ↓ from 100 mg to 40 mg over 3 weeks in 1 patients; In another 6 patients, P stopped in a median of 10.5 days, range (1–21 days) before symptoms onset	NM	Died (5) & survived (2)
8–15 [23]	NM	Primary brain tumour (8)	Dexa ↓ over a median of 12.5 days, range (1–63 days)	Fever (4), nonproductive cough (4), productive cough (2), dyspnoea (7), chest pain (4); CXR: bilateral infiltrates (3), diffuse infiltrates (3), focal infiltrates (1), clear (1)	Died (3) & survived (5)
16 [24]	M/55	Primary brain tumour (glioblastoma multiforme)	Dexa ↓ from 16 mg qd to 2 mg qd over 8 weeks	Intermittent fever, nonproductive cough, progressive dyspnoea; CXR: bilateral interstitial infiltrates; PaO_2 (RA): 51 mmHg	Treated with intravenous cotrimoxazole; survived
17 [24]	F/74	Primary brain tumour (meningioma)	Dexa ↓ from 12 mg qd to 4 mg qd over 2 weeks	Intermittent fever, nonproductive cough; CXR: bilateral interstitial infiltrates; PaO_2 (RA): 45 mmHg	Treated with intravenous cotrimoxazole; survived
18 [24]	M/50	Primary brain tumour (astrocytoma)	Dexa ↓ from 16 mg qd to 1 mg qd over 8 weeks	Fever, nonproductive cough, dyspnoea; CXR: bilateral interstitial infiltrates; PaO_2 (RA): 73 mmHg	Treated with intravenous cotrimoxazole; mechanical ventilation; survived
19 [24]	M/75	Primary brain tumour (glioblastoma multiforme)	Dexa ↓ from 16 mg qd to 4 mg qd over 6 weeks	Fever, nonproductive cough, bloody diarrhoea; CXR: clear; PaO_2 (RA): 89 mmHg	Treated with intravenous cotrimoxazole; survived
20 [25]	M/24	ACTH- producing metastatic bronchial carcinoid	Serum cortisol ↓ from 138 pg/ml to 18 pg/ml over 54 days	Fever, nonproductive cough, weakness, sweats; CXR: bilateral fluffy infiltrates; PaO_2 (RA): 40 mmHg	Treated with intravenous cotrimoxazole; mechanical ventilation; died of malignancy
21 [26]	F/38	Endogenous Cushing's syndrome	Metyrapone 750 mg qd added 1 day before symptoms onset	Productive cough, dyspnoea; CXR: right lower upper lobe infiltrates; PaO_2 (RA):31 mmHg	Treated with intravenous cotrimoxazole; mechanical ventilation; died
22–28 [32]	M/F 4:3 Mean (SD) age 53.1 (13.6)	ITP (2), GN (2), bullous pemphigoid (1), endogenous Cushing's syndrome (1), and renal transplantation (1)	Reduction of steroid but details of tailing regimen was not mentioned	An upsurge of lymphocyte counts from the reduction of immunosuppression (median 300/μL, range 290 to 740/μL) to the onset of IRD (median 1500/μL, range 600 to 5620/μL)	Treated with steroid as anti-PJP therapy in 7 (100%); mechanical ventilation in 6 (85.7%), died in 3 (42.9%)
29	M/33 (Our patient)	Systemic lupus erythematosus/ dermato-myositis overlapping syndrome	P ↓ from 45 mg to 15 mg over 4 days	Fever, dyspnoea; CXR: increased perihilar infilitrates; lymphocyte count increased from 600 to 1300/μL	Treated with intravenous cotrimoxazole and steroid; survived

Note. Aza, azathioprine; CXR, chest radiograph; Dexa, dexamethasone; IRD, immunorestitution disease; ITP, immune thrombocytopenia purpura; IS, immunosuppression; GN, glomerulonephritis; P, prednisolone; PCP, *Pneumocystis jiroveci* pneumonia; RA, room air.

Prognosis

- Despite treatment, still significant mortality
- Better survival (86% - 92%) in AIDS patients in comparison with non AIDS patients (51-80%)
- Prevention is essential in the groups at risk

Prevention

- Prevention of nosocomial transmission
  - ? Need of single room/ airborne isolation
- Use of chemoprophylaxis

HIV infected patients

- IDSA guideline : HIV infected adults/adolescents, including pregnant women and those on HAART, should receive chemoprophylaxis if $CD_4 < 200/\mu L$ or oropharyngeal candidiasis
- $CD_4 < 14\%$ should be considered
- Primary and secondary prophylaxis can be discontinued in those responded to HAART with $CD_4 > 200/\mu L$ for at least 3 months

Non HIV immunocompromised

- TMP-SMZ many side effects e.g. rash, haematological. NNH for severe adverse events requiring discontinuation was 32
- NNT was equal to NNH when the risk for PCP = 3.5%
- Benefit should be balanced with the risk of severe adverse events and the attack rate of PCP

Non HIV immunocompromised

- Solid organ cancer
  - Prophylaxis in those receiving high dose steroid
- Haematologi malignancies
  - ALL
  - Those treated with T cell depleting agents
  - CHOP-14, CHEOP-14 regimes
  - Considered in other regimes if have other risk factors e.g. chronic lung disease

Non HIV immunocompromised

- HSCT recipients - Allogenic
  - Prophylaxis from engraftment until 6 months post HSCT and throughout all periods of immunosuppression for those receiving immunosuppressive therapy/ have chronic CVHD
- HSCT recipients – Autologous
  - Intense conditioning regimes or graft manipulation
  - Those recently receiving fludarabine or cladribine

Non HIV immunocompromised

- Transplant recipients
  - Lung, heart, heart-lung recipients : lifelong
  - Liver : 6 months to 1 year
  - Renal : Minimum of 4 months and for another 3-4 months after a rejection episode. Should be extended (6-12 months) in those received lymphocyte depleting monoclonal antibody or antithymocte globulin

Non HIV immunocompromised

- Connective disease disorder
  - Wegener granulomatosis while on daily steroid
  - ? Dermatomyositis, polymyositis or SLE with known risk factors for PCP e.g. high dose steroid, interstitial lung disease
  - N.B. TMP-SMX can be administered in patients with up to 25mg of methotrexate per week. Need to receive folate supplementation (1mg/day) or leucovorin on the day after receiving methotrexate

Chemoprophylaxis regime

- TMP-SMX is the most studied and 1st choice in HIV infected/non HIV immunocompromised hosts
- Protection rates excellent, 89 – 100%

Prophylactic regimen against *Pneumocystis* pneumonia

	Medication	Dose and Route	Comments
First choice	Trimethoprim + sulfamethoxazole	80–160 mg daily 400–800 mg daily orally or intravenous	Contraindication in cases of allergy to sulfa drugs
	Trimethoprim + sulfamethoxazole	160 mg 3 times a week 800 mg 3 times a week orally or intravenous	
Alternative choice	Dapsone	100 mg daily orally	Contraindication in cases of G6PD deficiency Possible cross-reaction with sulfa allergy
	Dapsone + pyrimethamine	50 mg daily orally 50 mg per week + leucovorin 25 mg per week	Contraindication in cases of G6PD deficiency Possible cross-reaction with sulfa allergy
	Atovaquone	750 mg 2 times daily orally	Bioavailability increased with high-fat meal
	Pentamidine	300 mg monthly	Administrate in decubitus to optimize lung distribution

Resistance and prophylaxis failure

- Mutation prevalence in the DHPS (dihydropterorate synthetase) gene increased in the past years
- Have been associated with failure of TMP-SMX ad dapsone prophylaxis
- Mutation in the dihydrofolate reductase, the target enzyme of trimethoprim and pyrimethamine have also been recognized

Summary

- Common, severe opportunistic infection
- Evolving understanding of lifecycle and pathogenesis and thus the taxonomy
- Presentation tends to be more acute/ severe in non HIV immunocompromised host than AIDS patients
- Chest Xray is insensitive and HRCT is a better choice
- BAL +/- immunofluorescent monoclonal antibody staining is the preferred method for microbiological diagnosis

Summary

- TMP-SMZ is the treatment of choice/prophylaxis in HIV/ Non HIV patients. However, does need treatment that is effective with fewer side effects
- Use of corticosteroid is beneficial in AIDS patients with moderate to severe disease. Controversial in non HIV hosts
- Need of airborne isolation remains controversial
- Remained difficult to quantify / measure risk in non HIV immunocompromised patients