症例 2

# 食道がん化学療法中に出現した肺陰影

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【年齢・性別】60 歳，男性
【主訴】発熱，低酸素血症
【既往歴】脳出血（52 歳，左上下肢の筋力低下と痺れが軽度残存）
【家族歴】父：大腸癌（90 歳時）

【現病歴】

（X-5）月に嚥下困難，嘔吐の精査として実施された消化管造影検査で，食道壁の異常を指摘され当院を受診し，精査の結果，食道癌（cT3N2M0 StageIII）と診断された．上部消化管内視鏡検査では，門歯から 27-36cm に内腔狭窄を伴う亜全周性の 2 型腫瘍，門歯から 40cm に壁内転移がありいずれも生検で扁平上皮癌と診断された．術前の心臓超音波検査で心収縮能の低下を指摘され，他院で精査となり，慢性心不全，心房細動の診断でベータ遮断薬，抗凝固薬，利尿剤の投与が開始された．

（X-3）月に当院で試験開胸が実施されたが，腫瘍が左気管枝に浸潤しており T4 と診断し胃瘻造設のみで手術終了となった．食道癌の治療は放射線化学療法を実施することとなり，X 月 5 日までの 6 週間に放射線照射を 58Gy/29fr（食道，外照射）実施，（X-2）月下旬と（X-1）月下旬にそれぞれ 5-FU を 1239mg/body×4 日/サイクル（シスプラチン投与はなし）投与した（制吐剤としてデキサメサゾンを（9.9mg＋6.6mg×3 日）/サイクル併用）．

X 月 3 日から微熱があり誤嚥性肺炎疑いでセフメタゾールの投与が開始された（治療開始前に採取された喀痰培養からは感受性良好の *Klebsiella pneumoniae*，メチシリン感性の *Staphylococcus aureus* が検出され，血液培養 2 セットは陰性であった）．X 月 5 日から低酸素血症を認め，酸素投与を要する状況となり，以前から貯留していた右胸水の穿刺排液が実施された．X 月 7 日に高熱を伴うようになり感染症科にコンサルトがあった．

【身体所見（X 月 7 日）】

（一般）体温 38.7℃，意識 清明，心拍数 140/分，血圧 120/60mmHg，呼吸数 32/分（頭部）眼瞼結膜に貧血・出血なし．眼球結膜黄染なし．高度の口内炎，口唇炎あり．（頸部）リンパ節腫脹なし．（心音）リズムは絶対不整．2LSB に最強点を持つ Levine II/VI の収縮期雑音を聴取．（呼吸音）右下肺野呼吸音減弱．吸気時に左中下肺野に fine crackle を聴取．（腹部）平坦・軟．腸音正常．圧痛なし．肝脾腫なし．（背部）両側肋骨脊柱角部に叩打痛なし．（四肢）下腿浮腫なし．関節腫脹なし．

【血液検査所見（X 月 7 日）】

WBC 7200/μL（Meta 1%，Band 30%，Seg 64%，Lymph 1%，Mono 2%，Baso 1%，Eos 1%），RBC $3.39\times10^6$/μL，Hb 9.9g/dL，Hct 29.9%，MCV 88.2fL，Plt $194\times10^3$/μL，Alb 1.6g/dL，BUN 27.0mg/dL，Cr 0.81mg/dL，T.Bil 0.5mg/dL，LDH 401IU/L，AST 64IU/L，ALT 46IU/L，CRP 30.14mg/dL，Glu 99mg/dL，Na 141mEq/L，K 4.7mEq/L，Cl 106mEq/

Fig. 1

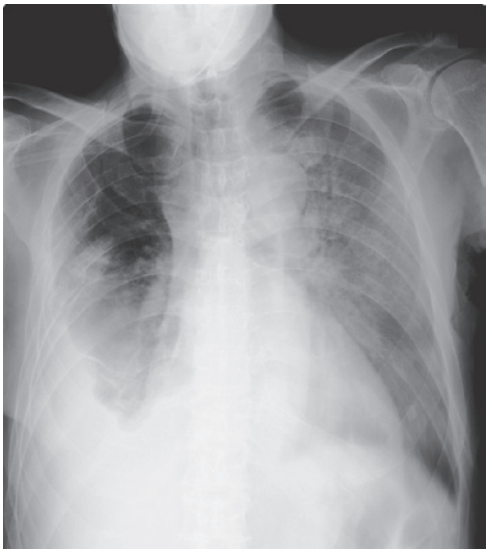
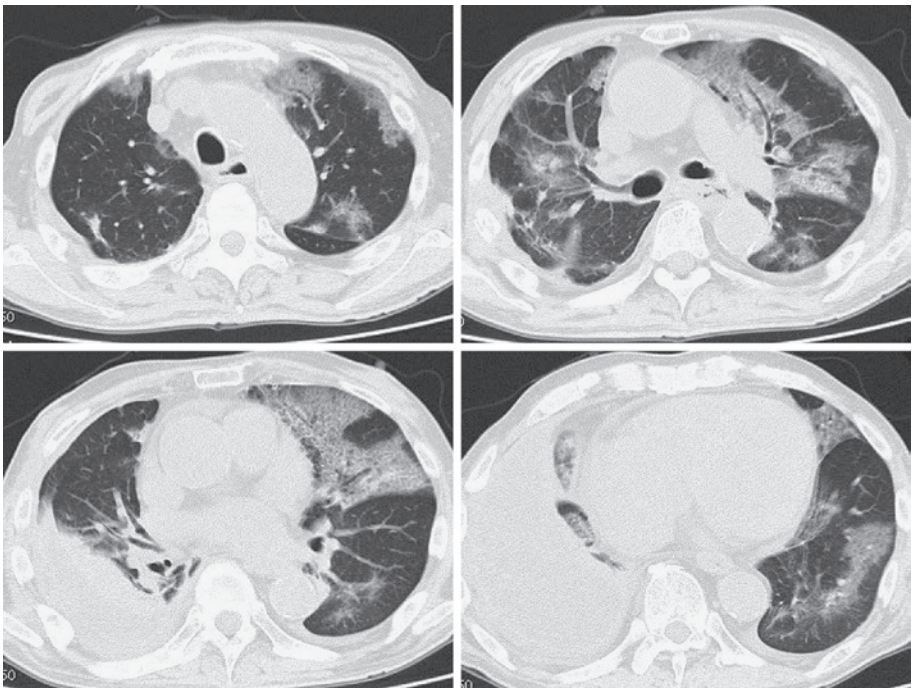


Fig. 2



L，BNP 456pg/mL（前回検査（1か月前）：386.0pg/mL），β-D-グルカン　163.6pg/mL（前回検査（2日前）：48.9pg/mL）

動脈血液ガス（マスク酸素5L/分）：pH　7.480，$PaCO_2$ 38.0Torr，$PaO_2$ 83.4Torr，$HCO_3^-$ 27.7mEq/L

【胸部X線検査（X月7日）】X月3日と比較して右下肺野の胸水貯留によるものと思われる濃度上昇の範囲は減少しているが，左肺野に広範なスリガラス状陰影が新たに出現している（Fig. 1）．

【胸部CT（X月5日）】左優位に両肺に小葉単位の濃淡を伴うスリガラス陰影が認められ，スリガラス陰影内に微細網状影がみられる．上肺では末梢優勢の分布が認められる．右優位に両側胸水貯留がある（Fig. 2）．

【コンサルト後経過】

基礎疾患に心房細動，慢性心不全を有する食道癌放射線化学療法中の患者に生じた発熱および低酸素血症，広範な肺陰影の鑑別診断として細菌性肺炎，非細菌性肺炎（Herpes simplex virus（HSV）口唇炎を伴うHSV肺炎，ニューモシスチス肺炎など），放射線肺臓炎，肺水腫，血管内カテーテル関連血流感染症などの医療関連感染症を検討した．診断目的に血液培養2セット，喀痰培養の再検，口唇潰瘍拭い液および喀痰のHSV-PCR検査，喀痰*Pneumocystis jirovecii*-PCR検査を提出した．また，再度，右胸水の穿刺排液を行い培養検査，細胞診検査を提出した（生化学検査では漏出性胸水であった）．喀痰グラム染色ではグラム陰性桿菌が優位に観察されたため，セフメタゾール耐性のグラム陰性桿菌による細菌性肺炎の可能性を考えタゾバクタム・ピペラシリン4.5g 8時間毎静注の投与を，β-D-グルカン高値から末梢カテーテル関連血流感染症によるカンジダ血症の可能性を考えミカファンギン 100mg 24時間毎静注の投与を，口唇炎を伴う間質性の肺炎像からHSV肺炎の可能性を考えアシクロビル 5mg/kg 8時間毎静注の投与を開始した．肺間質性陰影とβ-D-グルカン高値からニューモシスチス肺炎の可能性も検討したが，抗がん剤投与に伴う間欠的なデキサメサゾン投与を除いてはステロイド製剤や免疫抑制剤の投与はなく，その他の細胞性免疫不全をきたす患者背景もないことから可能性は低いと考え，経験的治療の対象とはしなかった．また，輸液量の調整と利尿剤による心不全の厳密な管理も併行して行った．以後も高熱と酸素化の持続的な悪化がみられ，X月8日以降はネーザルハイフロー 40L/50%酸素投与での管理となった．また，X月8日の気管支鏡検査で左主気管支に径3mm程度の瘻孔を指摘され，放射線療法に関連した食道気管瘻と考えられた．状態改善がないため，X月11日にはニューモシスチス肺炎疑いとしてトリメトプリム・サルファメトキサゾール

240mg/1200mg 8時間毎（トリメトプリム換算で15mg/kg/日）静注の投与，院内発症のレジオネラ肺炎の可能性を考えてのレボフロキサシン500mg 24時間毎静注の投与を開始した．

診断目的に提出した検査の結果は，血液培養は2セット中1セットのみから*Staphylococcus epidermidis*の検出（コンタミネーション），喀痰培養からはタゾバクタム・ピペラシリンに感受性を有する*Enterobacter cloacae*の検出，胸水培養は陰性，胸水細胞診では悪性細胞なし，口唇潰瘍拭い液および喀痰のHSV-PCRは陰性，喀痰*P. jirovecii*-PCR検査は陽性であった．これらの検査結果から，食道気管支瘻関連の細菌性肺炎（起因菌：*E. cloacae*）およびニューモシスチス肺炎疑いと診断し，X月12日以降はタゾバクタム・ピペラシリンおよびトリメトプリム・サルファメトキサゾールの投与のみ継続し，その他の抗微生物薬はすべて中止した．また，$AaDO_2$開大，低酸素血症を伴うニューモシスチス肺炎の併用療法として，プレドニゾロン60mg/日を5日間，30mg/日を5日間，15mg/日を10日間の投与を行った．なお，急性期の肺陰影は放射線照射野を超える範囲で認められたが，ステロイド投与が併存していた放射線肺臓炎の治療としても作用した可能性は否定できない．

X月12日以降は解熱し，呼吸状態も徐々に安定した．X月24日にはタゾバクタム・ピペラシリンの投与を中止した．（X+1）月1日にはトリメトプリム・サルファメトキサゾールの高用量投与は終了し，二次予防としてトリメトプリム・サルファメトキサゾール顆粒の1g/日の胃瘻からの投与とした．（X+1）月20日には酸素投与が不要な状態となり，（X+2）月3日に退院し，その後も呼吸状態の再増悪はみられなかった．

【考察】

基礎疾患に慢性心不全を有する食道癌の放射線化学療法後の発熱，肺陰影，低酸素血症の鑑別診断の検討に難渋した．患者背景からニューモシスチス肺炎の可能性は低いと当初は判断したが，進行する低酸素血症，β-D-グルカン高値，喀痰*P. jirovecii*-PCR陽性の結果から最終的にはニューモシスチス肺炎疑いとしての治療を他の治療と併行して行い，治癒を得た．固形腫瘍患者において，ニューモシスチス肺炎発症リスクがありST合剤の予防投与を検討すべき状況として，NCCN Guidelines™ Version 2.2011 Prevention and Treatment of Cancer-Related Infectionsでは，「脳腫瘍にテモゾロミド併用の放射線療法を行う場合」「プレドニゾロン換算で20mg/日以上の糖質コルチコイド剤投与を4週以上行う場合」が挙げられているが，本例はこれらには該当しない．関連しうるリスク因子としては抗がん剤投与時の制吐剤としてのデキサメサゾンの間欠大量投与があったこと，胸部への放射線療法実施であったことが挙げられる．

# “本症例の疑問点”から“研究的考察”へ

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## はじめに

*Pneumocystis* は1909年にCarlos Chagasによってモルモットの肺に感染する病原体として見出された．当初トリパノソーマの一種として *Schizotrypanum cruzi* と命名されたが，その後，チェコの病理学者Otto Jiroveciにより，1930-40年にヨーロッパで栄養失調の小児の間で流行した「急性形質細胞肺炎」の原因病原体としての *Pneumocystis* が記載された[1]．「急性形質細胞肺炎」の病理検体2例はいずれも栄養失調の小児の剖検から得られた検体であり，当然のことながらHIV感染症やステロイドを含めた医原性免疫不全症は有していなかった．Mayo ClinicのHenchらが，関節リウマチ患者に「compound E」を投与し，それまで寝たきりであった関節リウマチ患者が1週間後に歩けるようにまで回復したことを報告したのが1948年の“Mayo Clinic Proceedings”である．1950年前後に，今日の医原性免疫不全症の端緒となるステロイド治療，ならびに免疫不全患者における感染症の病原体の1つである *Pneumocystis* が記載されていることは興味深い．

*Pneumocystis jirovecii* は未だ培養方法が確立されていないため，詳細な生態は明らかになっていない．固形臓器移植後の患者に *Pneumocystis* 肺炎（以下PcP）が集団発症したことも報告されており，免疫不全状態ではないヒトがリザーバーとなっている可能性も指摘されている（Fig. 1）．

## 臨床免疫学の進展

免疫学は分子生物学の進展を受けて長足の進歩を遂げ，その進歩は着実にベッドサイドの患者さんの元に届けられている．

まず抗体産生の多様性を確保する仕組みが明らかになり，「液性免疫（humoral immunity）」「細胞性免疫（cellular immunity）」という理解がなされた．これらは既に歴史的な意味合いを帯びたClassicな分類であるが，上記に「好中球減少症」を加えた三分類が「医原性免疫不全症」を理解する上では未だに有用である[2]．

免疫システムは，適切な場所で・適切な強度の炎症を・適切な期間起こすことが期待されている．病原微生物を排除した後に炎症が遷延すると，それは“collateral damage”として自らの臓器障害に結びつく．この「炎症を局所でコントロールする」T細胞として制御性T細胞が同定され，現在intensiveな研究の対象である．関節リウマチにおいてはマクロファージから持続的に産生されるTNF-αが制御性T細胞の機能不全を引き起こし，炎症の遷延に寄与している可能性が最近報告されている[3]．

T細胞サブタイプ（Th1，Th2，Treg，Th17…）の研究とともに，近年の進歩が著しい分野として自然免疫の理解が挙げられる．免疫システムは病原体構造の一部を直接認識する受容体（PRR：pattern-recognition receptor）を介して，その非＝特異的な初期反応を開始させている．例えば真菌細胞壁の一部であるβ-Dグルカンは，Dectin-1という細胞表面受容体からSyk pathwayを介した細胞内シグナリングを送り，免疫システムの初期応答に関与している[4]．

## ベッドサイドからベンチへ

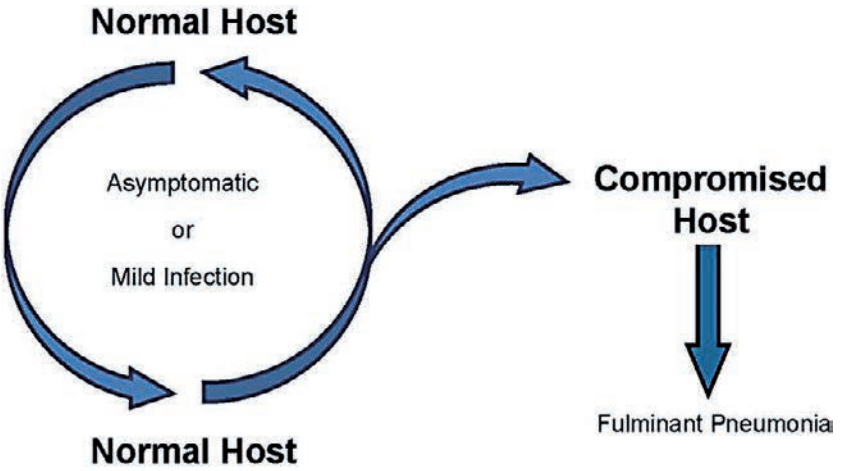
このような免疫学の爆発的進歩は，着実に実臨床の場を変えている．現在，免疫システムのHubにあると思われる分子に対して，モノクローナル抗体や経口小分子標的薬が続々と開発されており，同時に実臨床で多くの患者に上記のような新規薬剤が投与された結果が，さらにヒトの免疫システムの理解を進めるという「ベッドサイドからベンチへ」の流れも見られるようになってきた．

こうした新規薬剤は，開発の時点で，治療対象疾患や薬剤副反応について，十分に予想するのは困難であり，市販後調査によって思わぬ副作用（薬剤性間質性肺炎，ニューモシスチス肺炎，悪性腫瘍の誘発など）が明らかになることも多い．

## PcPと宿主免疫

HIV感染者においては，PcPを含めた日和見感染症の発症リスクはCD4数によって良好に予測することが可能であり，PcPを発症した患者のCD4カウントは90%が200未満であった．HIV感染者においてはCD4数がCD4陽性T細胞の機能を良好に反映

Fig. 1　*Pneumocystis jirovecii*

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すると考えられるだろう．また，CD4 数が 200 以上で PcP を発症する HIV 感染者の例では，ウィルス量（viral load）が非常に高い，PcP に罹患した既往を有する，などのリスク因子が見出される．

これまで“non-HIV”-PcP として一括されてきた疾患群は，実際には非常に heterogenous な集団である．古典的な高リスク群として造血幹細胞移植・固形臓器移植・悪性腫瘍（リンパ系造血器腫瘍）・膠原病や自己免疫性疾患などが同定されているが，これらは原疾患そのもの，更に治療薬によって様々な程度の免疫抑制を来たし，決して一括して考察できるものではない．

PcP 予防の第一選択薬である ST 合剤は広域抗菌薬であり，その少量長期投与は症例を選んで行うべきであろう．ST 合剤の使用は全身性エリテマトーデスの悪化と関連するという報告[5]や，fluconazole 耐性カンジダによる血流感染症と関連するという報告[6]もみられる．

しかし，non-HIV PcP は総じて HIV 関連 PcP よりも重症化しやすく，治療が遅れた場合の mortality も高い．これは PcP の病態生理の主要な部分が *Pneumocystis* 菌体の狭義の virulence によるものではなく，「*Pneumocystis* 菌体に対する肺の免疫反応である」ためと考察されている．しかし，HIV 関連 PcP で「CD4 が高い（より免疫力が保たれた？）状態で発症した PcP」が重症である，という報告はない．この事から，PcP に「罹患する」リスク因子と，PcP の「重篤度」を決めるリスク因子は異なるのではないかという仮説が導かれる．HIV 関連 PcP において，HAART 導入後に免疫再構築症候群として PcP が悪化するのは「*Pneumocystis* に反応しうる免疫も『立ち上がってくるため』」と理解できる．

### Non-HIV PcP の発症リスク

HIV 関連 PcP と同様，non-HIV PcP においても CD4 数をリスク因子として扱う試みはあるが[7]，HIV 関連 PcP ほどクリアな閾値を設定できない．免疫抑制剤を含む新規薬剤の臨床試験が多国籍で行われるようになり，また新規薬剤の市販後調査の結果などから，「PcP 発症リスクに地域差があり得ること」が注目されている（Fig. 2）．

さらに Hidden agenda として「既存の肺疾患があること」，即ち *Pneumocystis* 菌体が感染した後のクリアランスのメカニズムが障害されていることや，低栄養状態（本稿冒頭の如く，Jiroveci は栄養失調の子供の剖検肺から *Pneumocystis jirovecii* を同定したが，医療が進歩してなお「低栄養状態」が PcP リスクとして残ることは ironical である）などは，これまで着目されていない重要なリスク因子である可能性がある．

### 当該症例へのアプローチ

提示された症例は食道がんに対して放射線化学療法（レジメンの中に直接ステロイドや免疫抑制剤が含まれない）施行中に発症した肺炎で，ニューモシスチス肺炎として古典的なリスク因子（ステロイドの中等量以上の長期投与など）を有さないが，empirical な抗病原体治療に反応しないため，ニューモシスチス肺炎を想定した加療を行い改善した，というものである．本稿で「ステロイド（糖質コルチ

Fig. 2 ADVISORY COMMITTEE MEETING TOFACITINIB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS NDA 203214 BRIEFING DOCUMENT May 9, 2012

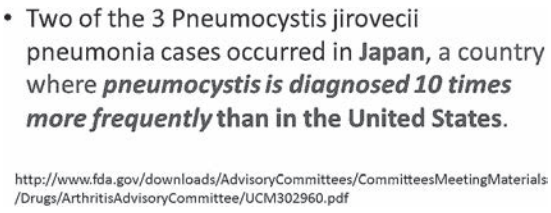
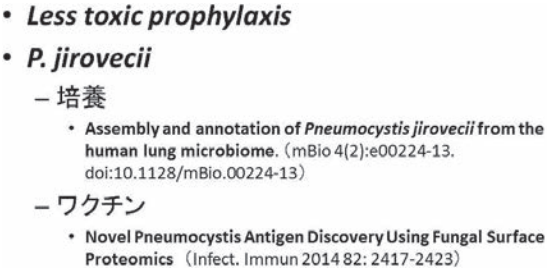



Fig. 3 Hope




コイド）の影響」については深く触れなかったが，使用するステロイドの種類（メチルプレドニゾロン，プレドニゾロン，デキサメタゾンなど），最大投与量，投与期間，治療対象とする疾患などによって「ステロイド誘発性 PcP」のリスクは異なると想像される．

将来的には PcP 治療薬として，抗 *Pneumocystis* 作用とともに「*Pneumocystis* に対する免疫反応を特異的に抑制する」作用を有した薬剤が期待されるが，それまでは本症例プレゼンターが行ったように，（PcP の診断閾値を低く保ち）「疑わしい」症例に治療量の ST 合剤とステロイドを投与するしかないだろう（Fig. 3）．

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Original article

# Predisposing factors, clinical characteristics and outcome of *Pneumonocystis jirovecii* pneumonia in HIV-negative patients

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ABSTRACT

*Pneumocystis jirovecii* (former *carinii*) pneumonia, is a life-threatening opportunistic infection occurring in immunocompromised hosts. The aim of this study was to investigate the predisposing factors, clinical features and outcome of *Pneumocystis* pneumonia (PCP) in HIV-negative patients. The medical records of 62 adult patients with PCP, hospitalized at the University Hospital of Heraklion, Crete, Greece during a 10-year period (2004–2013) were retrospectively reviewed. All patients were immunosuppressed prior to the development of PCP. Thirty one patients (50%) suffered malignant hematological disease, 16 (26%) solid tumor and 15 (24%) had chronic inflammatory disease. Only 17 (27%) had received long-term systemic corticosteroids. All had symptoms of pneumonia upon admission, while 12 (19%) were suffering respiratory failure. Twenty one (34%) had received trimethoprim/sulfamethoxazole (TMP-SMX) prophylaxis before the PCP onset. Eight patients (13%) were admitted to the ICU. Mortality attributable to PCP reached 29%. Mortality attributable to PCP was higher in patients with solid tumors. TMP-SMX prophylaxis failed in a significant portion of the present cohort. Hence, PCP should be included in the differential diagnosis in immunocompromised patients with symptoms from the respiratory tract even if TMP-SMX has been given as prophylaxis.



## 1. Introduction

*Pneumocystis jirovecii* (former *carinii)* pneumonia is a relatively common, life-threatening opportunistic infection of the immunocompromised hosts [1,2].

Although *Pneumocystis* pneumonia (PCP) is the most common opportunistic infection in human immunodeficiency virus (HIV) infected patients, may also occur in individuals with other forms of immunosuppression, including those with hematological malignancies, solid tumors, organ transplant recipients and patients suffering from inflammatory conditions requiring chronic immunosuppression with corticosteroids or cytotoxic agents [2–8].

In developed countries, the incidence and mortality of PCP in patients with HIV infection has been reduced due to the introduction of prophylaxis against *P. jirovecii* and the highly active antiretroviral therapy [2,9–11]. In contrast, the incidence of PCP among non-HIV patients has increased [9,11], as well as the need for hospitalization and intensive care unit (ICU) admission, while mortality is high (30%–50%), remaining unchanged over the last two decades [2,10,12–17].

Several studies have compared clinical manifestations of PCP in patients with and without AIDS [10,14,16,17], while others have tried to determine risk factors for PCP development in non-HIV patients. However, few data have been published on the impact of different types of immunosuppression on clinical presentation and outcome of PCP in non-HIV patients [15,18].

Improved knowledge of presenting symptoms, risk factors and identification of patients who need primary prophylaxis may help to reduce the PCP high mortality rate among non-HIV patients. Hence, the aim of the present study was to describe the underlying

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disorders and risk factors facilitating the PCP development, as well as the clinical presentation and factors influencing the outcome.

## 2. Patients and methods

The medical records of HIV-negative adult patients admitted to the University Hospital of Heraklion, Crete, Greece and diagnosed with PCP from January 2004 through to May 2013 were retrospectively reviewed.

Eligible for inclusion in the study were patients having clinical and radiological signs of pneumonia and positive results of direct fluorescent antibody staining for *P. jirovecii* in samples of induced sputum or bronchoalveolar lavage (BAL) fluid using indirect immunofluorescence microscopy with monoclonal antibodies (MONOFLUO TM, *Pneumocystis carinii* IFA-test kit, BIORAD).

Data collected from the patients' medical records included demographic information, past medical history, presenting signs and symptoms, laboratory and imaging results, treatment (antimicrobial and steroid treatment, *P. jirovecii* prophylaxis), need for mechanical ventilation, need for ICU admission and outcome.

PCP was considered as cause of mortality when death occurred during the diseases' treatment without other identified causes.

### 2.1. Definitions

Systemic inflammatory response syndrome (SIRS): 2 or more SIRS criteria [19].

Respiratory failure: hypoxemic (type I) if the arterial oxygen tension ($P_aO_2$) was lower than 60 mm Hg with a normal or low arterial carbon dioxide tension ($P_aCO_2$) or hypercapnic respiratory failure (type II) if the $PaCO_2$ was higher than 50 mm Hg with a low $P_aO_2$.

Fever: a body temperature elevation over 37.8 °C,
Neutropenia: absolute neutrophil count <1000 neutrophils/μL
Lymphopenia: absolute lymphocyte count <1500 cells/μL
Use of corticosteroids: equivalent of >20 mg prednisone per day for >30 days
Hypoxemia: inadequate level of oxygen in the blood. defined as a $PaO_2 < 80$ mm Hg

## 3. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows Version 17.0 (Chicago, IL, USA). Descriptive statistics for continuous variables are expressed as median (range) and categorical variables are presented as number and percentage (unless otherwise stated). Analysis of variance or Kruskal–Wallis tests (as applicable) were applied to continuous variables to determine if differences existed among the 3 cohorts (hematological malignancy vs. solid tumor vs. chronic inflammatory/autoimmune disease). Chi-square or Fisher's exact tests were conducted to assess differences between the 3 cohorts on categorical variables. For bivariate analysis, categorical variables were compared using the chi-square test, or Fisher's exact test when appropriate, while continuous variables were compared using Student's *t*-test or non-parametric Mann–Whitney *U* test (for not normally distributed variables). Multivariate analysis, using logistic regression model, was performed to determine the variables associated with mortality. Variables with a *p*-value <0.05 by bivariate analysis were included in the logistic regression analysis. The 0.05 *p*-value cut-off for inclusion in the multivariate analysis was chosen due to the small number of events (deaths) in this cohort.

All *p*-values were two sided, and statistical significance was accepted for *p*-value <0.05.

## 4. Results

### 4.1. Epidemiology and clinical characteristics

During the 10-year study period 62 patients with *P. jiroveci* positive sputum or BAL samples were identified by microscopy.

The mean age (standard deviation) of the patients was 65.2 ± 13.7 years. All 62 patients were immunosuppressed at the time of PCP development. Thirty one patients (50%) suffered hematological malignancies, 16 (26%) solid tumor, and 15 (24%) had chronic inflammatory disease. Regarding the type of immunosuppressive treatment, 26 (42%) patients were treated with chemotherapy, 17 (27%) had received chemotherapy and steroids and 13 (21%), had received long-term systemic corticosteroids only. Table 1 summarizes the immunosuppressive conditions in patients who suffered from PCP.

Twenty-nine patients (47%) had received steroids before the development of symptoms. Median time of steroid treatment was 40.5 days (range: 4–2190). In 8 out of 29 patients treated with steroids the dose was lowered before the onset of PCP, while in 10, PCP was diagnosed after the steroid treatment was withdrawn. The median time between the end of steroid treatment and the onset of PCP was 9.5 days (range: 2–51).

### 4.2. Clinical presentation and laboratory values of PCP on admission

Upon admission all patients had symptoms of pneumonia. Fever (52%) and cough (40%) were the two most common signs followed by dyspnea (32%). Half of the patients had more than 2 SIRS criteria (Table 2). The median time interval between the onset of symptoms

**Table 1**
Immunosupressive conditions associated with *Pneumocystis girovecii* pneumonia.

| Condition | No of patients (%) |
|---|---|
| Hematologic malignancy | 31 (50) |
| AML | 11 (18) |
| non-Hodgkin lymphomas | 6 (10) |
| Multiple myeloma | 5 (8) |
| CLL | 4 (6) |
| CML | 1 (2) |
| ALL | 1 (2) |
| Hairy-cell Leukemia | 1 (2) |
| Myelodysplastic syndrome | 1 (2) |
| Hodgkin lymphomas | 1 (2) |
| Solid tumor | 16 (26) |
| Lung cancer | 11 (18) |
| Breast cancer | 2 (3) |
| Stomach cancer | 1 (2) |
| Colon cancer | 1 (2) |
| Cervical cancer | 1 (2) |
| Chronic inflammatory disease/autoimmune disease | 15 (24) |
| Reumatoid arthritis | 7 (11) |
| Sarcoidosis | 2 (3) |
| Pulmonary fibrosis | 2 (3) |
| Ankylosing spondylarthritis | 2 (3) |
| Pemphigus | 1 (2) |
| Monoclonal gammopathy of undetermine significance | 1 (2) |
| Type of immunosuppressive treatment | |
| Chemotherapy alone | 26 (42) |
| Steroids + chemotherapy | 17 (27) |
| Long-term steroids | 13 (21) |
| Transplantation | 3 (5) |

AML: Acute myeloid leukemia, CLL: Chronic lymphocytic leukemia, CML: Chronic myelogenous leukemia, ALL: Acute lymphocytic leukemia.

**Table 2**
Demographics and clinical characteristics of 62 patients with *Pneumocystis jirovecii* pneumonia.

| Characteristic | Total ($n = 62$) | Hematological malignancy ($n = 31$) | Solid tumor ($n = 16$) | Chronic inflammatory/ autoimmune disease ($n = 15$) |
|---|---|---|---|---|
| Male gender | 43 (70) | 24 (77) | 10 (62.5) | 9 (60) |
| Comorbidities | 33 (53) | 10 (32)[b] | 9 (56)[b] | 14 (93)[b] |
| Number of comorbidities[a], mean (SD) | | 0.7 (±1.2)[b] | 0.9 (±0.9)[b] | 2.4 (±1.2)[b] |
| Co-infection | 16 (26) | 10 (32) | 1 (6) | 5 (33) |
| Duration of symptoms before admission | 10 (0–32) | 10 (4–32) | 8 (0–26) | 15 (3–25) |
| Steroid use | | | | |
| PCP during lowering dose | 8/29 | 6/18 | 0 | 2/11 |
| PCP after stoppage | 10/29 | 7/18 | 0 | 3/11 |
| Duration of steroid use | 40.5 (4–2190) | 10.5 (4–1820) | 47 (20–70) | 210 (39–2190) |
| Duration from steroid stoppage to PCP | 9.5 (2–51) | 6.5 (2–13) | 51 | 10 |
| SIRS on admission | 31 (50) | 17 (55) | 7 (44) | 7 (47) |
| Symptoms/signs | | | | |
| Fever | 32 (52) | 20 (64) | 6 (37.5) | 6 (40) |
| Cough | 25 (40) | 10 (32) | 6 (37.5) | 9 (60) |
| Dypsnea | 20 (32) | 7 (22.5) | 8 (50) | 5 (33) |
| Haemoptysis | 8 (13) | 6 (19) | 2 (12.5) | 0 (0) |
| Skin rash | 12 (19) | 5 (16) | 1 (6) | 6 (40) |
| Respiratory failure | 12 (19) | 3 (10) | 5 (31) | 4 (27) |
| Days from admission to diagnosis | 8.5 (3–79) | 11.5 (3–53) | 9 (3–32) | 7 (3–79) |
| Type of pneumonia | | | | |
| Interstitial | 48 (77) | 27 (87)[c] | 13 (81)[c] | 8 (53)[c] |
| Alveolar | 14 (23) | 4 (13) | 3 (19) | 7 (47) |
| Pleural effusion | 22 (35) | 13 (42) | 7 (44) | 2 (13) |
| Neutropenia | 18 (29) | 17 (55)[b] | 1 (6)[b] | 0 (0)[b] |
| Lymphopenia | 31 (50) | 17 (55) | 9 (56) | 5 (33) |
| Hypoxia | 23 (37) | 10 (32) | 5 (31) | 8 (53) |
| Arterial ph | 7.47 (7.27–7.55) | 7.48 (7.41–7.55) | 7.48 (7.39–7.50) | 7.43 (7.27–7.50) |
| LDH | 303 (87–1274) | 333.5 (87.0–1211.0) | 298 (168–1274) | 301 (150–475) |
| Albumin | 3.45 (2.20–4.70) | 3.35 (2.20–4.70) | 3.10 (2.40–3.80) | 3.5 (2.30–4.00) |
| Need for MV | 8 (13) | 2 (6.5) | 5 (31) | 1 (7) |
| ICU admission | 9 (14.5) | 2 (6.5) | 2 (12.5) | 5 (33) |
| Prophylaxis | 21 (34) | 15 (48)[b] | 3 (19)[b] | 3 (20)[b] |
| Type of treatment | | | | |
| TMP-SMX without other antimicrobials | 28 (45) | 15 (48) | 7 (70) | 6 (40) |
| Adjunctive steroids | 50 (81) | 22 (71) | 13 (70) | 15 (100) |
| Duration of hospitalization | 24 (3–117) | 34.5 (9–117) | 20 (3–44) | 21 (3–100) |
| Death attributable to PCP | 18 (29) | 8 (26) | 8 (50) | 2 (13) |

SD: Standard deviation; SIRS: Systemic Inflammatory Response Syndrome; MV: mechanical ventilation; ICU: Intensive Care Unit; TMP-SMX: Trimethoprim/sulfamethoxazole; PCP: *Pneumocystis jirovecii* pneumonia.
[a] Other comorbidities other than hematological malignancy, solid tumor, or chronic inflammatory/autoimmune disease.
[b] $p$-value $< 0.001$.
[c] $p$-value $= 0.047$.

and hospital admission was 10 days (range: 0–32) and the median time from admission to PCP diagnosis 8.5 (3–79).

Upon admission, hypoxemia was present in 23 (37%) patients, while 12 (19%) were suffering from respiratory failure. Over than one-fourth (29%) suffered from neutropenia, whereas lymphopenia was more common (50%).

Twenty one patients (34%) had received only trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for PCP before the disease onset. Prophylaxis was more common in patients suffering from hematological malignancies ($p$-value $< 0.001$).

### 4.3. Radiographic findings

Chest radiographs revealed consistently abnormal findings in all patients and were categorized by the major and most prominent radiological pattern. Interstitial infiltrates was the most common feature in all types of immunosuppression being present in 48 patients (77%), while alveolar infiltrates were present in 14 (23%). Interstitial infiltrates were more common in patients with chronic inflammatory/autoimmune disease as compared to those with hematological malignancies and solid tumors. Twenty two (35%) had pleural effusion (Table 2).

### 4.4. Treatment and outcome

All 62 patients were treated with TMP-SMX for a total of 3 weeks. Fifty (81%) received steroids as adjunctive treatment (Table 2).

Eight patients (13%) with *P. jirovecii* related acute respiratory failure were admitted to the ICU; all required mechanical ventilation (MV).

The median length of hospital stay was 24 days (3–117). No differences between immunosuppressive condition and length of hospital stay were revealed.

The mortality attributable to PCP reached 29% (Table 2). The therapeutic use of steroids did not affect mortality (15 patients out of 50 who received steroids died vs. 3 out of 12 patients who did not receive steroids, $p$-value $= 0.999$).

For definition of PCP prognostic factors, data of the 18 patients who died were compared with data of the 44 patients who survived in the bivariate analysis. Solid tumor, need for MV, presence of SIRS criteria on admission, presence of pleural effusion, and respiratory failure were found to be associated with mortality (Table 3). However, in the multivariate logistic regression analysis, a tendency for increased mortality in patients with respiratory failure [OR: 6.45 (95% CI: 1.19–34.48), $p$-value $= 0.031$] has been found.

## 5. Discussion

This retrospective, 10-year period study of 62 non-HIV patients with PCP has revealed that the infection occurred in 33% of patients receiving TMP-SMX prophylaxis and that patients with solid tumors had a higher mortality rate than those with other immunosuppressive conditions. The type of immunosupression did not affect the clinical characteristics of the disease.

PCP is a life-threatening infection occurring in immunocompromised individuals. The most significant risk factors for PCP development in patients without HIV infection are steroid use, cancer (particularly hematological malignancy), hematopoietic stem cell or solid organ transplantation, organ rejection, treatment for certain inflammatory conditions (particularly rheumatic diseases), primary immunodeficiencies (eg, severe combined immunodeficiency), and severe malnutrition [2,15,18,20–23].

All patients in the present study had an established risk factor for PCP. The majority suffered from hematological malignancies with acute myeloid leukemia (AML) and non-Hodgkin lymphomas (NHL) being the most frequent and from solid tumors while, 24% had a chronic inflammatory or autoimmune disease. The risk of PCP is particularly high among patients receiving steroids in combination with cytotoxic agents. However, it is of interest that over than one third (42%) of the patients in the present study were receiving only chemotherapy, when PCP occurred. This finding is in accordance with previous studies examining PCP in cancer patients and may indicate that chemotherapy or even malignancy per se can increase the PCP risk [23,24].

Previous studies revealed differences between type of immunosuppression and clinical characteristics of the disease [18]. On the contrary, significant differences either in signs and symptoms or in laboratory values could not be found in the present study. The only significant difference was the frequency of pleural effusion, which was lower in patients suffering chronic inflammatory disease when compared to patients with malignancies. In general, pleural effusion is considered a rare finding in patients with PCP [1,2]. However, the present findings have shown that pleural effusion in non-HIV patients with PCP occurs frequently, especially in patients with malignancies, a finding reported also by others [18].

PCP prophylaxis with TMP-SMX is considered to be highly effective, with significant reduction of mortality and a 91% reduction in the occurrence of the disease in patients with hematological malignancies or after transplantation [25]. On the contrary, such data regarding patients with solid tumors and immunosuppressed patients with rheumatic diseases are lacking.

There are guidelines supporting PCP chemoprophylaxis in patients with hematological malignancies or solid tumors but are only referring to patients receiving concomitant steroid therapy [26]. The present study as well as others have shown that cancer patients who receive only chemotherapy are also at risk for PCP and could potentially benefit from chemoprophylaxis [18,23]. However, guidelines supporting PCP prophylaxis in this subgroup of patients are lacking. In our series only three patients with solid tumor received PCP chemoprophylaxis, while half of those with hematological malignancies did so.

Interestingly, failure of TMP-SMX prophylaxis occurred in a significant portion of patients of the present cohort (34%). This

**Table 3**
Bivariate analysis of clinical characteristics in relation to death attributable to *Pneumocystis jirovecii* pneumonia.

| Variable | Patients who died ($n = 18$) | Patients who survived ($n = 44$) | $p$-value |
|---|---|---|---|
| Male gender | 11 (61) | 32 (73) | 0.368 |
| Chronic inflammatory disease | 2 (11) | 13 (30) | 0.193 |
| Hematological malignancy | 8 (44) | 23 (52) | 0.576 |
| Solid tumor | 8 (44) | 8 (18) | 0.032 |
| Number of comorbidities, mean (SD) | 1.2 (±1.4) | 1.2 (±1.3) | 0.976 |
| Symptoms/Signs | | | |
| Fever | 8 (44) | 24 (55) | 0.470 |
| Cough | 6 (33) | 19 (43) | 0.473 |
| Dypsnea | 5 (28) | 15 (34) | 0.629 |
| Haemoptysis | 3 (17) | 5 (11) | 0.738 |
| Skin rash | 5 (28) | 7 (16) | 0.282 |
| Respiratory failure | 9 (50) | 3 (7) | <0.001 |
| Duration of symptoms before admission, median (range) | 11.5 (0–32) | 9.5 (0–26) | 0.872 |
| SIRS on admission | 14 (78) | 17 (39) | 0.011 |
| Type of pneumonia | | | |
| Interstitial | 15 (83) | 33 (75) | 0.476 |
| Alveolar | 3 (17) | 11 (25) | 0.326 |
| Presence of pleural effusion | 10 (56) | 12 (27) | 0.035 |
| Co-infection | 4 (22) | 12 (27) | 0.760 |
| Days from admission to diagnosis | 11.5 (3–53) | 8 (3–79) | 0.157 |
| Neutropenia (<1500/μL) | 6 (33) | 12 (27) | 0.633 |
| Lymphopenia (<1000/μL) | 10 (56) | 21 (48) | 0.576 |
| Hypoxia (<70 mmHg) at room air | 10 (56) | 13 (30) | 0.082 |
| Arterial pH | 7.46 (7.41–7.50) | 7.48 (7.27–7.55) | 0.539 |
| LDH | 304 (176–1274) | 302 (87–1211) | 0.318 |
| Albumin | 3.30 (2.30–3.90) | 3.45 (2.20–4.70) | 0.799 |
| Need for MV | 6 (33) | 2 (4.5) | <0.001 |
| ICU admission | 6 (33) | 3 (7) | 0.011 |
| Prophylaxis | 6 (33) | 15 (34) | 0.999 |
| PCP therapy | | | |
| TMP-SMX without other antimicrobials | 8 (44) | 20 (45) | 0.999 |
| TMP-SMX combined with other antimicrobials | 10 (56) | 24 (55) | 0.999 |
| Adjunctive steroids | 15 (83) | 35 (80) | 0.999 |

PCP: *Pneumocystis jirovecii* pneumonia; CT: computed tomography; MV: mechanical ventilation; SIRS: Systemic Inflammatory Response Syndrome; ICU: Intensive Care Unit; TMP-SMX: Trimethoprim/sulfamethoxazole
Bold numbers represent statistically significant results.

observation is consistent with some previous reports [4,27,28]. In a study by Saah et al., that documented a 20% failure of PCP prophylaxis in 476 HIV patients, the main predictor of failure was profound T-helper lymphocytopenia [27]. Furthermore, failure of primary or secondary anti-PCP prophylaxis is associated with a specific *P. jiroveci* genotype [28]. In the present study we were unable to reveal any predictor for prophylaxis failure.

Regarding PCP treatment, all patients of the present study received TMP-SMX as initial empirical treatment. Of interest, 81% of them received adjunctive steroid therapy. Whereas this approach has been proven to be helpful in patients with AIDS [29], it has not been validated in non − HIV immunocompromised patients. Despite the fact that there are some studies suggesting that steroids can be helpful as treatment of HIV-negative patients with PCP [29] the present study has shown that adjunctive corticosteroid therapy did not affect the prognosis at all, as previously reported by others [15,21,23]. However, this result needs to be confirmed by large randomized trials.

In the present study the mortality attributable to PCP reached 29%, being similar to that reported by several authors [7,12,18,20,23]. Evaluation of the parameters influencing outcome of the present PCP cases has shown that only respiratory failure was an independent predictive factor for mortality.

The present study has limitations. Firstly due to the relatively small number of cases, sufficient power might not have been present to demonstrate potential differences between type of immunosuppressive condition and clinical characteristics. Similarly, the relative small number of patients who died affects the statistical power to reveal potential predictors of outcome. Secondly the retrospective nature did not allow some variables to be recorded such as the number of CD4 cells and the total dose of steroids in all included patients.

In conclusion, all immunocompromised non-HIV patients with symptoms of pulmonary infection should be carefully evaluated for PCP. Mortality of this infection remains high. Limited data are available for the efficiency of PCP prophylaxis in solid tumors and immunosuppressed patients with rheumatic diseases. Hence, PCP should be included in the differential diagnosis even in patients receiving TMP-SMX prophylactically.

## Conflict of interest

The authors have no potential conflicts of interest.

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None.

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REVIEW ARTICLE

# *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients in the era of novel immunosuppressive therapies

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**Abstract** In human immunodeficiency virus (HIV)-infected patients, *Pneumocystis jirovecii* pneumonia (PCP) is a well-known opportunistic infection, and its management has been established. However, PCP is an emerging threat to immunocompromised patients without HIV infection, such as those receiving novel immunosuppressive therapeutics for malignancy, organ transplantation, or connective tissue diseases. Clinical manifestations of PCP are quite different between patients with and without HIV infections. In patients without HIV infection, PCP rapidly progresses, is difficult to diagnose correctly, and causes severe respiratory failure with a poor prognosis. High-resolution computed tomography findings are different between PCP patients with HIV infection and those without. These differences in clinical and radiologic features are the result of severe or dysregulated inflammatory responses that are evoked by a relatively small number of *Pneumocystis* organisms in patients without HIV infection. In recent years, the usefulness of PCR and serum $\beta$-D-glucan assay for rapid and noninvasive diagnosis of PCP has been revealed. Although corticosteroid adjunctive to anti-*Pneumocystis* agents has been shown to be beneficial in some populations, the optimal dose and duration remain to be determined. Recent investigations revealed that *Pneumocystis* colonization is prevalent, and that asymptomatic carriers are at risk for developing PCP and can serve as the reservoir for the spread of *Pneumocystis* by person-to-person transmission. These findings suggest the need for chemoprophylaxis in immunocompromised patients without HIV infection, although its indication and duration are still controversial. Because a variety of novel immunosuppressive therapeutics have been emerging in medical practice, further innovations in the diagnosis and treatment of PCP are needed.

**Keywords** *Pneumocystis jirovecii* pneumonia · Non-HIV-infected patients · Rheumatoid arthritis · $\beta$-D-Glucan · PCR

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## Introduction

*Pneumocystis jirovecii* pneumonia (PCP) is a potentially life-threatening fungal infection that is seen in immunocompromised individuals. Before the 1980s, PCP was recognized as a rare but fatal infection primarily among patients with acute leukemia and other hematological malignancies. In the 1980s, the worldwide epidemic of human immunodeficiency virus (HIV) dramatically increased the prevalence of PCP as one of its most common complications. Although PCP once increased explosively among HIV-infected patients, progress in anti-retroviral therapies and the use of routine prophylaxis against PCP has led to reduced rates of PCP in the HIV-infected population in most industrialized countries. However, PCP remains a significant cause of pneumonia in patients with other types of immunodeficiencies [1–4]. In particular, with the recent introduction of biologics and molecular-targeted agents for the treatment of rheumatic diseases, inflammatory bowel diseases (IBD), and malignancies, a rising incidence of PCP has been noticed [4–8].

PCP occurs in non-HIV patients with a variety of underlying diseases or conditions, including hematological malignancies, solid tumors, organ transplantations, and connective tissue diseases. The clinical manifestations of PCP are quite different between non-HIV patients and those with HIV infection and also between patients with different underlying diseases [8–13]. There are many issues to be solved concerning the diagnosis, treatment, and prophylaxis of PCP in non-HIV patients. In addition, ethnic differences in the incidences of PCP have been indicated [14, 15], which suggests an unknown mechanism of the pathogenesis. This article reviews the current understanding of the pathogenesis, clinical presentation, diagnosis, treatment, prophylaxis, and prognosis of PCP in the non-HIV population.

## Mycology

In 1909, Carlos Chagas first discovered *Pneumocystis* cystic forms in the lungs of guinea pigs. A year later, Antonio Carini found similar cysts in the lungs of rats. They first concluded that the cysts are a new species of trypanosome. In the 1940s, *Pneumocystis* was recognized as a pathogen for pneumonia in malnourished or premature infants. In 1952, Otto Jirovec, a Czech pathologist, first identified this organism as the cause of interstitial pneumonia in these infants. *Pneumocystis*, which was first classified as a protozoa, indeed shares some biological characteristics with protozoa [3]. Based on DNA sequence analyses, *Pneumocystis* is now classified as a fungus, although in contrast to other fungi it lacks ergosterol and is extraordinarily difficult to grow in culture. The whole genome analysis of *Pneumocystis* has been completed [3, 6]. In the recent nomenclature change, the form that infects humans has been renamed *Pneumocystis jirovecii* after Otto Jirovec [16]. A unique form of *Pneumocystis* has been identified in virtually every mammal, each with differing genetics and stringent host specificity. For example, the form that infects rats cannot infect humans and vice versa. Study of the life cycle and drug susceptibility of *Pneumocystis* has been hindered by the inability to isolate it in pure culture. Morphological studies revealed three distinct stages: the trophozoite (trophic form), in which it often exists in clusters, the sporozoite (precystic form), and the cyst, which contains several intracystic bodies (spores). The trophic form is 1–4 μm in diameter, and the mature cyst is 8–10 μm in diameter. During infection of the lung, the trophic forms predominate over the cyst forms by $\sim$10:1 [8–10].

## Colonization and transmission

Based on serological testing, most children acquire infection with *P. jirovecii* by age 4 [17, 18], but the rates of colonization were unclear until the investigations using polymerase chain reaction (PCR). In HIV-infected patients, the rates of colonization were reported to be as high as 69 % [19]. Recent evidence has revealed that the non-HIV population is also frequently colonized with *Pneumocystis* [20]. *Pneumocystis* colonization has been reported in infants, elderly patients with chronic obstructive pulmonary disease (COPD) and other lung diseases, patients undergoing immunosuppressive therapy, and healthcare workers [21–26]. In addition, Chilean investigators identified *P. jirovecii* in 65 % of the autopsied lungs of 77 healthy individuals, which provided convincing evidence that colonization of *Pneumocystis* is highly prevalent among the general population [27].

Earlier expert opinions suggested that PCP develops after reactivation of latent infection, but a growing body of evidence indicates that de novo exposure from individuals with PCP or those who are colonized with *Pneumocystis* may result in person-to-person transmission [28–31]. In HIV-infected patients who experienced two episodes of PCP, genetically distinct isolates were associated with each episode, which suggests that the recurrent episodes of PCP were caused by reinfection rather than by reactivation of a latent infection [21, 32]. In addition, in a large outbreak of PCP in renal transplant recipients, genotyping of the *P. jirovecii* isolates indicated airborne transmission from an index case at the outpatient clinic and the ward [22]. The results of these genetic epidemiological studies using genotyping support person-to-person spread of *Pneumocystis* [6, 7].

*Pneumocystis*-colonized individuals may not only serve as a reservoir for disease transmission but also pose a risk for developing PCP [23]. Previous studies have found disease onset following colonization, usually with *Pneumocystis* with the same genotype [4–8, 23]. Mori and colleagues performed PCR for *P. jirovecii* on respiratory specimens from 82 patients with rheumatoid arthritis (RA) and identified 9 (11 %) as asymptomatic carriers. Three among the 9 carriers developed PCP within 1 month after the PCR testing [33]. These findings suggested that a colonized individual can be at risk for rapid development of PCP.

## Host response to *Pneumocystis*

The host immune response during PCP involves complex interactions between $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, alveolar macrophages, and soluble mediators that facilitate clearance of the infection [34, 35]. The trophic forms of *Pneumocystis* adhere tightly to alveolar type I epithelial cells. In response to proliferation of *Pneumocystis*, uptake of the organisms by macrophages occurs

through multiple receptor systems, including the action of mannose receptors that interact with gpA/major surface glycoprotein (MSG) on the surface of *Pneumocystis*, and the interaction between *Pneumocystis* β-D-glucan and the macrophage surface receptors, dectin-1 and toll-like receptor 2 [3]. Opsonic proteins, including IgG, in the alveolar spaces also participate in this uptake process. Alveolar macrophages are known to play a key role in the recognition, phagocytosis, and degradation of *Pneumocystis* [36]. In addition, various proinflammatory cytokines and chemokines that are released from activated macrophages and epithelial cells are essential for the optimal elimination of the organisms [2, 36, 37].

$CD4^+$ T cells have crucial activities in host defense against *Pneumocystis*. $CD4^+$ T cells proliferate in response to *Pneumocystis* antigens and generate interferon (IFN)-γ, which induces further recruitment of macrophages. Interleukin (IL)-8, which is released from epithelial cells and macrophages, strongly enhances the recruitment of neutrophils that not only contribute to the organism clearance but also mediate lung injury through the release of proteases and oxygen radicals. Severe PCP is characterized by neutrophilic lung inflammation that may result in diffuse alveolar damage, impaired gas exchange, and respiratory failure. In acquired immunodeficiency syndrome (AIDS)-associated PCP, IL-8 and neutrophil levels in bronchoalveolar lavage (BAL) fluid correlate closely with impaired oxygenation and mortality [38]. In non-HIV patients with PCP, the IL-8 levels in BAL fluid were higher than in HIV-infected patients and correlated with the oxygenation index [39]. These findings indicate that, once the host immune response is excessive, pulmonary inflammation potently contributes to lung injury, which is the outline of PCP in non-HIV patients [3, 6, 7].

During PCP, pulmonary inflammation more potently contributes to lung injury than direct effects of the organism. The inflammatory response is triggered by the surface antigens of the organism, such as MSG and β-D-glucan [2, 3, 11]. Mice with severe combined immunodeficiency (SCID) lacking functional T and B lymphocytes have spontaneous *Pneumocystis* infection by 3 weeks of age. In spite of progressive infection, the SCID mice show normal oxygenation and lung function until the late stages of the disease [40]. When the immune systems in these animals are reconstituted with the use of intact spleen cells, an intense T-cell-mediated inflammatory response ensues, resulting in substantially impaired gas exchange. Similarly, in HIV-positive patients, the initiation of antiretroviral therapy during the course of PCP treatment is often associated with a paradoxical worsening of PCP with a relapse in their symptoms and a deterioration in their respiratory status. This phenomenon, which is known as the immune reconstitution syndrome (IRS), is a consequence of the recovery of immune function resulting from antiretroviral therapy. These observations indicate that the development of lung injury requires cellular immune response besides *Pneumocystis* infection [3].

## Clinical features of *Pneumocystis* pneumonia in patients with various underlying diseases

PCP develops in patients with immunosuppression or immunomodulation in response to the underlying disease or its treatment. The underlying diseases or conditions of PCP in non-HIV patients include hematological malignancies, solid tumor, organ or hematopoietic stem cell transplantation (HSCT), and connective tissue diseases under immunosuppressive treatment [12]. Risk assessments for PCP in these population are somewhat complex and cannot be clearly determined by $CD4^+$ lymphocyte counts as in patients with HIV infection [41]. The most common treatment-related risk factors include the use of corticosteroids, purine analogues, anti-CD52 and anti-CD20 monoclonal antibodies, calcineurin inhibitors, and tumor necrosis factor (TNF)-α antagonists (Table 1).

The clinical features of PCP are quite different between HIV-infected patients and those without HIV infection. PCP in non-HIV patients is characterized by an abrupt onset of respiratory insufficiency. In non-HIV patients, it takes about a week from the onset of fever and dry cough until the development of respiratory failure, whereas PCP in HIV-infected patients has a more gradual disease course that lasts for 2 weeks to 2 months. Respiratory

**Table 1** Immunosuppressive agents associated with the development of *Pneumocystis* pneumonia

| | |
|---|---|
| Corticosteroids | Purine analogs |
| Alkylating agents | Azathioprine |
| Cyclophosphamide | Cladribine |
| Temozolomide | Fludarabine |
| Antibiotics/immunosuppressants | Mycophenolate mofetil |
| Bleomycin | TNF-α inhibitors |
| Antimetabolites | Adalimumab |
| Cytarabine | Etanercept |
| Fluorouracil | Infliximab |
| Methotrexate | Monoclonal antibodies |
| Calcineurin inhibitors | Alemtuzumab |
| Cyclosporine | Rituximab |
| Tacrolimus | Tocilizumab |
| mTOR inhibitors | CTLA4-Ig[a] |
| Everolimus | Belatacept |
| Sirolimus | |

[a] CTLA4-Ig: fusion protein composed of the extracellular domain of cytotoxic T-lymphocyte antigen 4 (CTLA-4)

insufficiency is usually more severe in non-HIV patients than in the HIV-infected population. *Pneumocystis* is more difficult to detect in non-HIV patients because of the smaller numbers of organisms in the lungs. The outcomes of PCP are more favorable in HIV-infected patients than in those without HIV infection. The mortality rates of PCP range from 30 % to 60 % among non-HIV patients, whereas the rates are 10–20 % among the HIV-infected population [2, 9, 10].

These differences in the clinical features of PCP are thought to be caused by the differences in the immune response of the host. Limper and colleagues evaluated the numbers of inflammatory cells and organisms in BAL fluid during PCP in patients with various underlying disorders [11]. They observed that HIV-infected patients with PCP had significantly greater numbers of organisms and fewer neutrophils in BAL fluid and less severe oxygenation impairment compared to other immunocompromised patients with PCP, which suggested that the severity of PCP could be determined by the inflammatory response rather than by the load of the organisms [11]. After this epoch-making investigation, it has become common understanding that PCP in the non-HIV population is characterized by severe inflammatory response evoked by a relatively small number of organisms.

## Hematological malignancy

Hematological malignant disorders, especially leukemia and lymphomas, are the most common underlying immunosuppressive conditions of PCP in HIV-negative patients [2, 4]. HSCT for these disorders is associated with an increased risk for PCP [42–44]. A retrospective cohort study that was conducted at the M.D. Anderson Cancer Center during 1990–2003 revealed that, among 80 episodes of PCP in 79 patients, 53 (66 %) episodes occurred in patients with hematological malignancies and 23 (29 %) in HSCT recipients [42]. Sepkowitz and colleagues described that PCP in patients with hematological malignancies was characterized by poor prognoses with in-hospital mortalities of 34–53 % [43].

Some specific therapeutic regimens are associated with an increased level of cellular immunosuppression and a consequently increased risk of PCP. Most of the patients received corticosteroids at the time of the PCP diagnosis. In addition, fludarabine and other purine analogues, commonly used in the treatment of chronic lymphoid malignancies, lead to severe and prolonged T-cell immunosuppression, predisposing to PCP and other opportunistic infections. Other cytotoxic agents that have been found to be associated with an increased risk of PCP include cytarabine, vincristine, cyclophosphamide, and methotrexate. Rituximab, which targets $CD20^+$ B cells, also increases the risk of PCP in patients receiving CHOP-based chemotherapy [4, 45]. Although tyrosine kinase inhibitors are also used for treatment of hematological malignancies, there has been only one lethal case of PCP reported in a patient who received dasatinib, a multikinase inhibitor, for chronic myeloid leukemia [46].

Today, guidelines have been published in which trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis is recommended in patients with some hematological malignancies and in HSCT recipients [47]. Routine prophylaxis is suggested in patients with acute lymphoblastic leukemia or in those treated with T-cell-depleting agents or high-dose corticosteroids. With the routine use of PCP prophylaxis, the attack rate was 0.17 % for patients with acute lymphoblastic leukemia, 0.31–0.34 % for lymphoma patients, and 0.32 % for patients with leukemia other than acute lymphoblastic leukemia [4]. In HSCT recipients, the attack rate was as high as 5–15 % without prophylaxis. A meta-analysis of randomized controlled trials, including 1,245 patients who had undergone autologous bone marrow transplants or who had hematological malignancies, showed that the prophylaxis markedly reduced the PCP-related mortality [48]. PCP in patients with hematological malignancies may be becoming a preventable disease as in HIV-infected subjects.

## Solid tumors

Among solid tumors, primary or metastatic brain tumors, lung cancer, and breast cancer are associated with higher risks of PCP, whereas PCP rarely occurs in patients with malignancies of the digestive organs [43]. The attack rate for those with primary or metastatic brain tumors was reported to be 1.3–1.7 % [43]. In patients with solid tumors, corticosteroid use and radiotherapy were considered risk factors for the development of PCP [49]. In contrast, PCP has been rarely reported in cancer patients treated with platinum-based and other regimens of chemotherapy alone [4]. It remains to be determined whether novel molecular-targeted therapeutics are associated with a risk of PCP.

## Solid organ transplant recipients

PCP is one of the critical issues in recipients after transplantation of solid organs [4, 50]. The reported incidence of PCP among heart transplant recipients has varied widely, from 5 % to 41 %. Among liver transplant recipients, 10–11 % of patients developed PCP. PCP is more frequent in the recipients of heart–lung transplants, with reported rates of 16–43 % in the absence of prophylaxis [4].

Until the early 2000s, the risk of PCP was estimated to be lower in renal transplant recipients than in recipients of

other organ transplants. Subsequently, several outbreaks of PCP among renal transplant recipients have been reported [22, 51, 52]. This dramatic change might be associated with the introduction of a new generation of immunosuppressants, rituximab and mycophenolate mofetil (MMF), in addition to corticosteroids and calcineurin inhibitors, which achieved marked reduction of the rejection rate. The increase in PCP could be associated with the use of MMF, which targets lymphocyte proliferation [53]. There has been an increasing number of reports of PCP in renal transplant recipients receiving everolimus and other mammalian target of rapamycin (mTOR) inhibitors. De Castro and colleagues [54] identified 11 cases of PCP in renal transplant recipients and found that the duration of corticosteroid treatment, the use of mTOR inhibitors, and lymphocytopenia at the time of prophylaxis discontinuation were risk factors for PCP.

### Connective tissue diseases other than rheumatoid arthritis

Among connective tissue diseases, Wegener's granulomatosis is associated with a higher risk for the development of PCP: the incidence of PCP was 6 % in a series of 180 patients followed between 1968 and 1992 [55]. This higher incidence may be the result of daily corticosteroid with additional immunosuppressive agents [56].

There is also a higher incidence of PCP among patients with dermatomyositis or polymyositis (PM/DM) and those with systemic lupus erythematosus (SLE) [57]. In these patients, high-dose corticosteroid and immunosuppressive therapies are associated with the risk of PCP [58, 59]. In patients with these diseases, PCP could develop early in the course of the immunosuppressive therapy, the risk of which might be associated with lymphopenia before the initiation of corticosteroid treatment [60].

### Rheumatoid arthritis

PCP used to be uncommon in patients with RA, with reported frequencies of 0.02 % in RA patients compared to 0.89 % in patients with Wegener's granulomatosis [59] and 8 % in HIV-infected patients with lymphocytopenia [61]. Since the introduction of low-dose methotrexate (MTX) as an important therapeutic for RA in the 1980s, increasing numbers of RA patients have developed PCP, although the accurate incidence remains unclear [62]. Tokuda and colleagues [63] evaluated the clinical features of PCP in RA patients who were treated with MTX. Compared to PCP in HIV-infected patients, PCP in those with RA developed more rapidly, showing higher serum CRP levels and severe oxygenation impairment. In most of the RA patients with PCP, *Pneumocystis* could not be detected microscopically, requiring PCR for the microbiological diagnosis [63]. No significant immunosuppression was observed in RA patients with PCP in terms of the preserved concentrations of serum IgG and $CD4^+$ lymphocytes in peripheral blood. All the 14 RA patients with PCP received TMP-SMX with corticosteroids, and 2 (14 %) were deceased [63].

TNF-α inhibitors and other biologics were introduced for the treatment of RA around 2000, after which PCP was reported in those receiving the biologics [14]. The Japanese postmarketing surveillance (PMS) program for infliximab, a monoclonal antibody against TNF-α, showed that the incidence of PCP was 0.4 % in the 5,000 patients enrolled [64], which is more than ten times higher than the reported incidence of this infection in data from Western studies of this agent [15]. An epidemiological survey in the United States revealed no increase in the incidence of PCP after the introduction of biologics [65]. Compared to the infliximab-treated patients without PCP, patients with PCP were significantly older, had a higher prevalence of coexisting pulmonary disease, and were treated with a higher daily dose of prednisolone [66]. Interestingly, the median time to develop PCP was 8.5 weeks from the first infusion of infliximab, and 16 (76 %) patients developed PCP within 14 weeks after the first infusion [66]. This pattern is quite different from that seen in the patients treated with corticosteroid and classical immunosuppressants such as cyclophosphamide in whom the risk of PCP increases in proportion to the duration of the administration [66].

Similar results were shown in PMS of adalimumab, etanercept, and tocilizumab. During the PMS in Japan for etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, PCP developed in 15 (0.2 %) patients in the 7,091 patients evaluated [67]. Because 6 (24 %) of the 25 patients died, a particular concern was raised that Japanese patients treated with TNF-blocking agents might have an increased risk of the fatal lung complication, PCP. The PMS for tocilizumab, an anti-IL-6 receptor monoclonal antibody, and adalimumab, a fully human $IgG_1$ anti-TNF monoclonal antibody, also revealed comparable data. Kameda and coworkers evaluated 26 patients who developed acute respiratory failure with diffuse ground-glass opacity (GGO) on chest computed tomography (CT) while receiving a biological agent [68]. The final diagnoses for 26 patients examined were definite PCP for 13 patients, probable PCP for 11, and MTX-induced pneumonitis for 2 patients. In all the PCP cases, the onset was around 3 months after the first administration of the biological agent [68]. PCP in those treated with a biological agent was characterized by severe respiratory failure, requiring oxygen supplementation in 17 (71 %) patients and mechanical ventilation in 6 (25 %). The clinical outcome, however, was favorable with treatment with TMP-SMX and corticosteroids, with only 1 (4 %) deceased patient [68].

### Inflammatory bowel diseases

Patients with IBD, ulcerative colitis and Crohn's disease, are effectively treated with corticosteroids with or without cyclosporine or TNF-$\alpha$ inhibitors, which may increase the risk of PCP. There have been some reports of severe or fatal episodes of PCP in patients with IBD under immunosuppressive therapies [69, 70]. In PMS in Japan, only a few cases of PCP were reported in patients receiving infliximab for IBD [71]. This low incidence of PCP could be owing to the younger average age of the patients and the low prevalence of preexisting lung diseases.

## Diagnosis

### Clinical presentation

PCP classically presents with fever, cough, and dyspnea, which are not specific to PCP. Compared with PCP in HIV-infected patients, PCP in non-HIV population usually develops more rapidly and causes more severe oxygenation impairment. Physical examination is nonspecific, and the pulmonary auscultation is often normal, even in the presence of significant hypoxemia [2].

### Microbiological diagnosis

Because *Pneumocystis* cannot readily be cultured in the laboratory, the microscopic demonstration of the organisms in respiratory specimens has been the gold standard for the diagnosis of PCP [2, 4, 6]. Cysts can be stained with Grocott–Gomori methenamine-silver, which has good specificity, but its sensitivity is not satisfactory. Because the trophic forms predominate over the cyst forms, Giemsa and Diff-Quik staining of the trophic forms is supposed to have high sensitivity, but it is not consistent, depending upon the skill and experience of the observer.

In non-HIV patients, bronchoscopic procedures for the diagnosis of PCP are often difficult because of rapidly progressive respiratory insufficiency [5, 8]. In addition, PCP patients without HIV infection have a lower burden of *Pneumocystis* than those with AIDS, which leads to difficulty in detecting the organisms by microscopic observation [5]. PCR has 94–100 % sensitivity and 79–96 % specificity for the diagnosis of microscopically positive PCP [72–75]. Because of its high sensitivity, PCR is increasingly used for the microbiological diagnosis of PCP. Although BAL fluid is the optimal specimen for PCR analysis, induced sputum has been shown to be acceptable. Moreover, recent investigation has shown that *Pneumocystis* DNA can be detected by PCR in oropharyngeal washes and nasopharyngeal aspirates [5, 8].

Nested or conventional PCR, which uses PCR primers for the gene for *Pneumocystis* mitochondrial large-subunit ribosomal RNA, is a technically established method that is widely used in clinical practice [76]. Because PCR is known to often produce false-positive results, partly because of *Pneumocystis* colonization in elderly patients, especially those with COPD and other chronic lung diseases, a positive PCR of *P. jirovecii* does not always mean the infection or PCP [77]. In patients with positive PCR results in BAL fluid or sputum but with negative smears, clinical management of the disease remains a challenge [2]. Azoulay and colleagues [78] described that, among immunocompromised patients with lung infiltrates and positive PCR results, positive and negative predictive values were 51.5 % and 98.7 %, respectively. Considering the disease severity, positive PCR results in immunocompromised patients with hypoxemia and typical radiologic findings could be sufficient to start treatment of PCP. As PCR shows a high negative predictive value, negative PCR results allow for withdrawal of anti-*Pneumocystis* therapy [78].

Quantitative real-time PCR assays have been reported to be more promising for the diagnosis of PCP than conventional PCR assays that lack specificity in distinguishing the disease from colonization [79, 80]. Flori and coworkers [72] compared the sensitivity and specificity of standard staining, conventional PCR, and real-time PCR using 173 BAL fluid specimens from 150 patients (19 HIV-infected and 131 non-HIV patients). They found that the sensitivity and specificity of the techniques were 60 % and 100 % for staining, 100 % and 87.0 % for conventional PCR, and 100 % and 84.9 % for real-time PCR, respectively [72]. Matsumura and coworkers described that the sensitivity and specificity for discriminating definite PCP from colonization were 100 % and 80.0 %, respectively, at a cutoff value of 1,300 copies/ml; the values for discriminating probable PCP from colonization were 66.7 % and 73.3 %, respectively, at a cutoff value of 340 copies/ml [81]. Although real-time PCR displayed high accuracy for discriminating colonization from PCP, the DNA sequences targeted for PCR and the cutoff values used in these assays have not been standardized.

### Serological diagnosis

Because BAL is often difficult for patients with respiratory failure, serological diagnoses of PCP have been investigated. (1 → 3)-$\beta$-D-glucan ($\beta$-D-glucan) is derived from the cell wall of several fungi including *Pneumocystis* [82]. The $\beta$-D-glucan assay was originally developed in Japan for diagnosis of deep-seated mycosis and has been best studied for *Candida* and *Aspergillus* spp. [82]. Although it is not specific for *Pneumocystis*, measurement of serum

β-D-glucan level has been used for the diagnosis of PCP [83–86]. There remain, however, a couple of issues to be solved [83]. First, at least four different methods of measurement are commercially available, and they are not always compatible with each other [82]. Fungitec G-Test MK, a kinetic chromogenic assay using the serum of *Tachypleus tridentatus* as the lysate, and β-D-glucan Test Wako, an endpoint chromogenic assay using the serum of *T. tridentatus* as the lysate, are widely used in Japan. When the same sample is assayed, the former method usually produces a higher value than the latter. In Western countries, Fungitell, a kinetic chromogenic assay using the serum of *Limulus polyphemus* as the lysate, is widely used. Second, false-positive results caused by a number of factors, such as the administration of immunoglobulin, bacteremia, hemodialysis, surgical gauze exposure, and certain antibiotics, are known. Third, the cutoff value for the diagnosis of PCP still remains to be determined. In a retrospective case–control study of 295 patients with suspected PCP who had microscopy of BAL fluid for PCP and serum β-D-glucan assay with β-D-glucan Test Wako, Tasaka and colleagues found a cutoff value of 31.1 pg/ml with a sensitivity of 92 % and a specificity of 86 % for detecting PCP [85]. On the other hand, Watanabe and coworkers evaluated the diagnostic value of the assay in 111 patients with AIDS and described a cutoff value of 23.2 pg/ml with a sensitivity of 96.4 % and a specificity of 87.8 % [86]. de Boer and colleagues [87] assessed the diagnostic accuracy in 31 non-HIV immunocompromised patients who were suspected of having PCP based on the clinical presentation and chest imaging. They showed that β-D-glucan measured by Fungitell was a reliable indicator for PCP with a sensitivity of 0.90 and specificity of 0.89 at the 60 pg/ml cutoff level [87]. Because a meta-analysis revealed a high sensitivity for PCP [83], the β-D-glucan assay could be useful at least for the screening of the disease. It remains controversial whether or how serum β-D-glucan assay is utilized for the assessment of treatment response or the prediction of the outcome of PCP [13, 87, 88].

Although elevated levels of serum lactate dehydrogenase (LDH) and KL-6 and lower levels of plasma *S*-adenosylmethionine were noted in patients with PCP, the diagnostic significance of these markers has been shown to be inferior to that of β-D-glucan [85, 87, 89, 90]. Because this field has been intensely investigated, a standard for the serological diagnosis of PCP will be established in the near future.

### Radiologic presentation

On chest radiographs, PCP typically presents with bilateral or diffuse GGO. The chest radiograph is sometimes normal. High-resolution computed tomography (HRCT) typically shows diffuse GGO with patchy distribution. In some patients with PCP, GGO is distributed in the subpleural lung parenchyma, whereas peripheral sparing of GGO occurs in others [91, 92].

Differences in the radiological characteristics of PCP in patients with various underlying disorders had not been intensively investigated until Tokuda and colleagues reported the imaging features of PCP in patients with RA and PCP in HIV-infected patients [63]. In half the RA patients with PCP, HRCT revealed diffuse GGO distributed in a panlobular manner; that is, GGO was sharply demarcated from the adjacent normal lung by interlobular septa (Fig. 1a). The other half of the RA patients with PCP presented diffuse GGO without sharp demarcation, which is characteristic of PCP in HIV-infected patients (Fig. 1b) [63]. In contrast, diffuse GGO distributed in a panlobular manner was rarely observed in PCP patients who received a biological agent for RA [68]. This difference in the HRCT patterns may result from difference in the host immune response.

PCP in patients with hematological malignancies is characterized by GGO with patchy consolidation along the bronchovascular bundle on HRCT (Fig. 1c) [93]. Although cystic lesions were observed in similar percentages for both patients with HIV infection and those with malignancies (Fig. 1d) [93], other investigators described that cyst formation is a characteristic CT finding of PCP in AIDS patients [94]. This discrepancy might be because only limited data are available for the CT findings of PCP in patients with malignancies.

## Treatment

Because of the high efficacy and the availability of oral and parenteral forms, TMP-SMX is the first-line agent for the treatment of mild to severe PCP in both HIV-infected and non-HIV patients [2, 4, 8, 95]. This therapy, however, is often complicated with adverse events, which include hepatotoxicity, nephrotoxicity, bone marrow depression, and skin rash, that sometimes become an obstacle to the completion of the treatment. The recommended daily dose is trimethoprim 15–20 mg/kg plus sulfamethoxazole 75–100 mg/kg [95]. Because this dose recommendation is not based on a randomized controlled trial, the optimal dose of TMP-SMX remains unclear. A retrospective investigation by Thomas and colleagues revealed a good outcome with trimethoprim 10 mg/kg/day plus sulfamethoxazole 50 mg/kg/day for PCP in HIV-infected patients [96]. Kameda and coworkers reported that 67 % of the rheumatic patients treated with TMP-SMX experienced adverse events, such as gastrointestinal and hematological disorders, and 38 % could not complete the treatment [68].

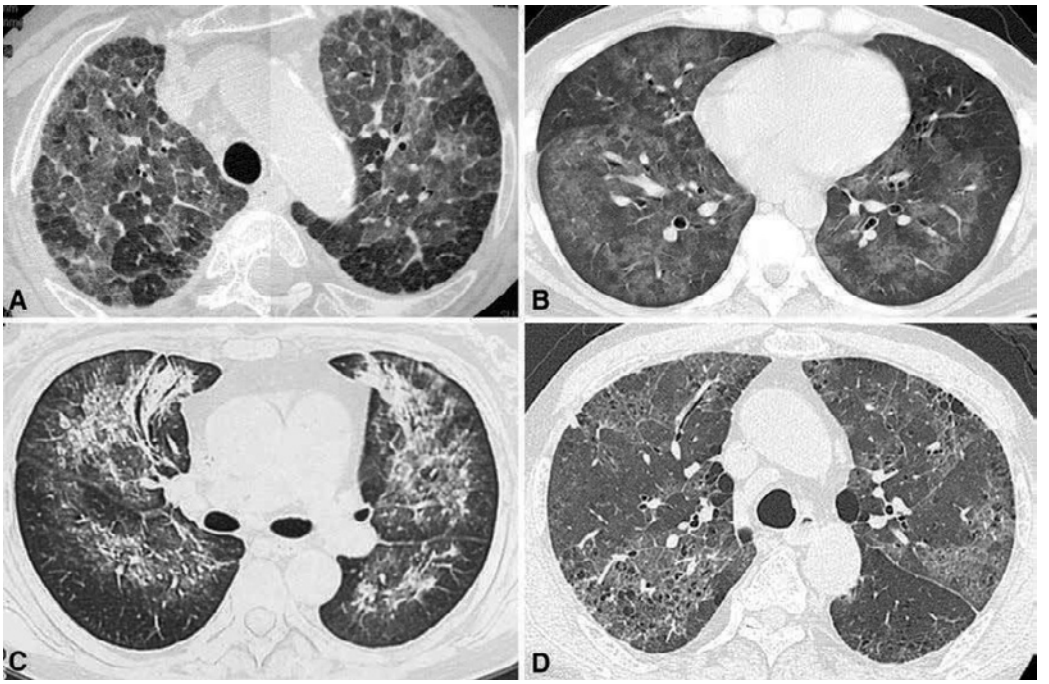


**Fig. 1** High-resolution computed tomography findings of *Pneumocystis jirovecii* pneumonia (PCP). **a** PCP in a patient with rheumatoid arthritis receiving methotrexate therapy. Diffuse ground-glass opacity (GGO) is distributed in a panlobular manner, in which GGO is sharply demarcated from the adjacent lung by interlobular septa. **b** PCP in a patient with human immunodeficiency virus (HIV) infection. Diffuse GGO is distributed in an inhomogeneous manner without sharp demarcation. Subpleural sparing is also indicated. **c** PCP in a patient with malignant lymphoma. Among GGO, patchy consolidation is located along the bronchovascular bundle. **d** PCP in a cancer patient who was receiving chemotherapy and high-dose corticosteroid. Cysts are observed within the affected area, suggesting that they were formed by PCP

In their case series, the clinical outcome was favorable with only 4 % of mortality, suggesting that a reduced dose of TMP-SMX may be sufficient for PCP in RA patients who were treated with a biological agent.

Intravenous pentamidine is the most studied drug as an alternative to TMP-SMX. Although pentamidine is about as effective as TMP-SMX, the incidence of adverse events, such as nephrotoxicity and dysglycemia, during treatment with pentamidine is even higher compared to TMP-SMX. Atovaquone, which is less effective but better tolerated than TMP-SMX, is as effective as pentamidine. Clindamycin-primaquine is the salvage regimen of choice for those patients who fail standard therapy with TMP-SMX or pentamidine [8, 10, 97].

Putative TMP-SMX drug resistance is an emerging concern. Because this drug is widely used not only for treatment but also for prophylaxis, the emergence of drug resistance is anticipated. The inability to culture *Pneumocystis* in a standardized culture system prevents routine susceptibility testing and detection of drug resistance. In other microorganisms, sulfa drug resistance has resulted from specific point mutations in the dihydropteroate synthase (DHPS) gene. Similar mutations have been observed in *P. jirovecii*, and its association with prior sulfa prophylaxis failure has been reported [98]. Prevalence of these mutations has been increasing to as high as 81 % [99], although there have been no data showing significant association between the DHPS gene mutations and treatment failure [4, 8].

The recommended duration of treatment is 21 days in HIV-infected patients and 14 days in non-HIV immunocompromised hosts. Recommendation for longer treatment in HIV-infected patients is based on the higher organism burden and slower clinical response, which may result in a higher risk of relapse after only 14 days of treatment. In non-HIV patients, extended treatment should be considered in case of severe immunosuppression, high organism burden, or prolonged clinical improvement [4, 8].

In the guidelines, the addition of corticosteroids is recommended for HIV-infected patients with PCP [95]. Adjunctive corticosteroid therapy is advocated for PCP patients with arterial oxygen pressure less than 70 mmHg because it could attenuate lung injury by blunting the inflammatory response initiated by the degradation and clearance of the organisms [95]. A systematic review showed a significant mortality-risk reduction with adjunctive

corticosteroids in HIV-infected patients with PCP when substantial hypoxemia exists [100]. In the non-HIV population, however, there have been no randomized studies on the use of adjunctive corticosteroids for PCP. Only a few retrospective studies have examined this matter [101–103]. Pareja and colleagues found that non-HIV patients with severe PCP who received 60 mg or more of prednisone daily demonstrated favorable outcomes compared to those maintained on a low-dose corticosteroid regimen [101]. They concluded that high-dose adjunctive corticosteroids might accelerate recovery in cases of severe PCP in adult non-HIV patients [101]. In another retrospective study, Korean investigators evaluated the outcomes of 88 non-HIV patients with moderate-to-severe PCP, comparing 59 patients with adjunctive corticosteroid use and 29 without [102]. As the survival analysis did not reveal any difference between the two groups, they concluded that adjunctive corticosteroid use might not improve the outcomes of moderate-to-severe PCP in non-HIV patients [102]. These diverse results may result from the heterogeneous background of the non-HIV subjects examined. Adjunctive corticosteroid use for PCP in a non-HIV patient should be considered after taking the background of the patient into account.

## Prophylaxis

Despite intensive treatment, the mortality of PCP remains high, which is the rationale for chemoprophylaxis. As already mentioned, there have been guidelines for prophylaxis against PCP for patients with hematological diseases and solid tumors and recipients of HSCT and solid organ transplantation [47, 104–106]. Although these guidelines are not based on a randomized controlled trial, they have been contributing to effective prophylaxis (Table 2). For immunocompromised patients with other underlying diseases, the indication and dosage for prophylaxis should be considered carefully, taking into account hepatotoxicity, bone marrow depression, and other side effects of TMP-SMX [107].

In renal transplant recipients, PCP prophylaxis is recommended, although its duration varies among the guidelines, with a range of 3–12 months after transplantation

**Table 2** Proposed indications for chemoprophylaxis against *Pneumocystis* pneumonia

| |
|---|
| General patients |
| Prednisone at least 20 mg for >4 weeks if patient has underlying immunosuppressive disorder or COPD [12, 107] |
| Cancer |
| Receiving corticosteroids [47] |
| Alemtuzumab during and for at least 2 months after treatment and CD4 >200 cells/ml [47] |
| Temozolomide and radiation therapy and until CD4 is >200 cells/ml [47] |
| Fludarabine and T-cell-depleting agent (e.g., cladribine) until CD4 >200 cells/ml [47] |
| All patients while receiving anti-leukemic therapy [47] |
| Connective tissue diseases |
| Wegener's granulomatosis treated with cyclophosphamide, especially if also receiving corticosteroids [55, 56] |
| Primary systemic vasculitis treated with corticosteroids and steroid-sparing agent (e.g., methotrexate) [113] |
| ANCA-associated vasculitis treated with cyclophosphamide and corticosteroids [114] |
| Rheumatoid arthritis treated with TNF-α inhibitors especially if on corticosteroids or other intensive immunosuppression [66] |
| Connective tissue diseases treated with prednisolone >20 mg per day or equivalent doses of corticosteroid for more than 2 weeks [111] |
| Hematopoietic stem cell transplantation |
| Allogeneic stem cell recipients for at least 180 days [47] |
| Autologous peripheral blood stem cell transplant recipients for 3–6 months after transplant [47] |
| All recipients for 6 months [104] |
| Recipients receiving immunosuppressive therapy or with chronic graft-versus-host disease (GVHD) for >6 months or the duration of immunosuppression [104] |
| Solid organ transplantation |
| Solid organ transplant recipients for at least 6–12 months after transplant [106] |
| Renal transplant recipients for a minimum of 4 months after transplantation [108] |
| Renal transplant recipients for 3–6 months after transplantation and at least 6 weeks during and after treatment for acute rejection [107] |
| Inflammatory bowel disease |
| Patients receiving TNF-α inhibitors especially if on corticosteroids or other intensive immunosuppression [70] |

*COPD* chronic obstructive pulmonary disease, *ANCA* anti-neutrophil cytoplasmic antibodies, *TNF-α* tumor necrosis factor-alpha

[108]. The mortality rate from PCP among renal transplant recipients was reported to be 5–33 % in the absence of prophylaxis [109]. From a survey of the United States renal transplant centers, 84 % of the centers use PCP prophylaxis. The incidence of PCP has been markedly reduced with TMP-SMX prophylaxis to <1 % in renal transplant recipients [109, 110]. However, occurrence of PCP even 10 years or more after transplantation has been documented [22] and, thus, lifelong prophylaxis is advocated for high-risk patients. To prevent an outbreak, when a single case of PCP occurs, 6 months of prophylaxis with TMP-SMX may be worth considering for all the recipients who shared the waiting space of the outpatient clinic [107].

PCP prophylaxis has been recommended in patients with Wegener's granulomatosis because of the high incidence of PCP among the patients [55]. Although there are no published guidelines, PCP prophylaxis should be initiated in patients with SLE or PM/DM who receive considerable immunosuppressive treatment. In high-risk patients with connective tissue diseases other than RA, TMP-SMX was used effectively as a primary prophylaxis against PCP and associated only with mild side effects, suggesting that the prophylaxis is reasonable [111–114].

Although PCP in patients with RA has become a critical issue, there is no explicit guideline for the prophylaxis. Komano and colleagues reported that the development of PCP in patients with RA treated with infliximab was best predicted by age (≥65 years), dosage of prednisolone (≥6 mg/day), and pulmonary comorbidities [66]. Because patients with two or three of the foregoing risk factors developed PCP more frequently than those with only one or none, they recommended that prophylaxis should begin in patients with two or three risk factors [66]. However, Green and coworkers described that, balanced against the serious adverse events that required discontinuation occurred in 3.1 %, PCP prophylaxis in non-HIV population is warranted when the risk for PCP is estimated to be higher than 3.5 % [48]. Because the risk for PCP in patients with RA has been estimated to be less than 0.5 % in Japan, the indication for prophylaxis should be considered carefully. Thomas and Limper suggested that RA patients treated with MTX only, MTX plus corticosteroids, or TNF-α antagonists only, should not be the subjects of chemoprophylaxis [115]. Prophylaxis should be limited to those receiving considerable immunosuppressive therapies, such as a TNF-α antagonist plus high-dose corticosteroid.

TMP-SMX is the first-choice prophylaxis in HIV-infected and in non-HIV immunocompromised hosts. The dosage usually recommended is one tablet (80 mg TMP and 400 mg SMX) daily or two tablets three times per week. A meta-analysis showed no difference in the rate of PCP infections after daily versus three-times-weekly prophylaxis [33]. Chemoprophylaxis is usually continued throughout the period of immunosuppression or so long as the risk lasts. Duration of the prophylaxis should be decided in a patient-based manner. In patients with RA or renal transplant recipients, a shorter period of prophylaxis may be sufficient [33, 116].

## Prognosis

Mortality in non-HIV patients with PCP is 30–60 %, whereas the mortality rate ranges from 10 % to 20 % during the initial episode of PCP in HIV-infected patients [2]. In non-HIV patients, mortality depends on the population at risk, with a greater risk of death among patients with cancer than among patients undergoing transplantation or those with connective tissue disease [12, 13, 101]. In addition, multivariate analyses revealed that low serum albumin levels and mechanical ventilation were independent predictors of mortality, which indicates that poorer general and respiratory conditions at diagnosis are associated with poor outcome of the patient [88, 117].

## Summary

There still remain many clinical issues regarding PCP in the non-HIV population. For example, it is controversial how to utilize PCR for the diagnosis, how to use serum β-D-glucan testing as a diagnostic aid, and how and when to use adjunctive corticosteroids. Further efforts by investigators are warranted for better management of the disease.

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