PREVALENCE, CLINICAL MANIFESTATIONS, TREATMENT OUTCOMES, COST OF TREATMENT AND HEALTH RELATED QUALITY OF LIFE (HRQoL) OF CHRONIC PULMONARY ASPERGILLOSIS (CPA) IN A TERTIARY REFERRAL HOSPITAL IN LAHORE, PAKISTAN

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by

WAQAS AKRAM

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LIST OF ABBREVIATIONS

CPA	Chronic Pulmonary Aspergillosis
SA	Simple Aspergilloma
CCPA	Chronic Cavitary Pulmonary Aspergillosis
SAIA	Sub-Acute Invasive Aspergillosis
ABPA	Allergic Broncho pulmonary Aspergillosis
IPA	Invasive Pulmonary Aspergillosis
CNPA	Chronic Necrotizing Pulmonary Aspergillosis
CFPA	Chronic Fibrosing Pulmonary Aspergillosis
TB	Tuberculosis
COPD	Chronic Obstructive Pulmonary Disease
BAL	Broncho Alveolar Lavage
ICU	Intensive Care Unit
CT	Computerized Tomography
GM	Galactomannan
NTM	Nontuberculosis Mycobacteria
PCR	Polymerase Chain Reaction
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
ERS	European Respiratory Society
ECMM	European Confederation of Medical Mycology
IDSA	Infectious Diseases Society of America
GFIF	Global Fungal Infection Forum
GAFFI	Global Action Fund for Fungal Infections
HRQoL	Health Related Quality of Life

SGRQ	St. George Respiratory Questionnaire
EOT	End of Treatment
USM	Universiti Sains Malaysia

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PREVALENSI, MANIFESTASI KLINIKAL, HASIL RAWATAN, KOS RAWATAN DAN KUALITI HIDUP BERKAITAN KESIHATAN (HRQoL) PESAKIT ASPERGILLOSIS PULMONARI KRONIK (CPA) DI SEBUAH HOSPITAL RUJUKAN TERTIER DI LAHORE, PAKISTAN

ABSTRAK

CPA ialah jangkitan progresif kronik yang memusnahkan tisu paru-paru pada pesakit yang tidak terjejas imun. CPA menyumbang dengan ketara kepada morbiditi, kematian dan peningkatan kos penjagaan kesihatan, walaupun, penyakit ini masih kurang didiagnosis di Pakistan. Terdapat kekurangan penyiasatan mengenai epidemiologi CPA, terapi antikulat optimum, tempoh terapi dan kos rawatan. Di samping itu, sehingga kini data tersedia adalah terhad mengenai manifestasi klinikal dan hasil CPA di Pakistan. Oleh itu, kajian retrospektif dan prospektif dua fasa telah dijalankan untuk menilai epidemiologi CPA, manifestasi klinikal, hasil rawatan, faktor risiko yang berkaitan dengan perkembangan, LOS yang berpanjangan, kematian, kos langsung rawatan, dan HRQoL pesakit CPA yang mendapat rawatan di Gulab Devi Hospital Dada, Lahore, Pakistan. Semasa fasa retrospektif (2017-2019), sejumlah 44,028 pesakit respiratori telah dianalisa. CPA diperhatikan dalam 248 (0.56 %) kes. Prevelansi CPA ialah 563/100,000 mengikut kriteria ESCMID/ERS. Seramai 218 pesakit CPA telah dimasukkan dalam fasa ini. Jenis CPA yang paling biasa ialah SA (56.0%) diikuti oleh CCPA (31.2%) dan SAIA (12.8%) masing-masing. Gejala yang paling biasa dalam pesakit CPA ialah batuk (95.0%), keletihan (92.7%), pengeluaran kahak (90.4%), demam (85.8%), hemoptisis (59.6%), dan penurunan berat badan (34.9%). TB (62.8%), NTM (30.7%), dan DM (29.8%) adalah penyakit umum yang paling biasa. Selepas CPA didiagnosis, semua pesakit telah dirawat dengan

itraconazole oral (n = 152, 69.7%), voriconazole (n = 15, 6.98%), dan amphotericin B (n = 51, 23.4%). Penambahbaikan klinikal diperhatikan dalam 122 (56.0%) pesakit manakala perkembangan positif radiologi dan mikrobiologi dilihat pada 115 (52.7%) dan 163 (74.7%) pesakit, masing-masing. Kadar kematian keseluruhan ialah 27.1%. Analisis regresi multivariate menunjukkan usia tua (NISBAH GANJIL: 2.53), jantina lelaki (NISBAH GANJIL: 3.40), BMI rendah (NISBAH GANJIL: 0.52), TB aktif (NISBAH GANJIL: 0.87), TB sebelumnya (NISBAH GANJIL: 1.36), sejarah merokok (NISBAH GANJIL: 2.64), COPD (NISBAH GANJIL: 5.31), DM (NISBAH GANJIL: 0.30), ILD (NISBAH GANJIL: 4.08) dan penggunaan steroid (NISBAH GANJIL: 1.96) sebagai peramal bebas CPA. Enam pembolehubah termasuk sejarah merokok (NISBAH GANJIL: 0.97), CCPA (NISBAH GANJIL: 0.84), TB sebelumnya (NISBAH GANJIL: 0.35), COPD (NISBAH GANJIL: 0.89), DM (NISBAH GANJIL: 4.23), dan, malignan hematologi (NISBAH GANJIL: 0.08) adalah dikaitkan dengan penginapan hospital yang berpanjangan. Sebelas faktor bebas yang dikaitkan dengan kematian pada analisis multivariate ialah umur (NISBAH GANJIL: 0.17), fenotip CCPA (NISBAH GANJIL: 0.25), penggunaan steroid (NISBAH GANJIL: 0.65), HRF (NISBAH GANJIL: 5.68), konsolidasi paru-paru (NISBAH GANJIL: 17.08), penebalan pleura. (NISBAH GANJIL: 8.31), bola kulat (NISBAH GANJIL: 0.04), DM (NISBAH GANJIL: 2.34), TB sebelumnya (NISBAH GANJIL: 3.07), TB aktif (NISBAH GANJIL: 0.06) dan malignan hematologi (NISBAH GANJIL: 0.08). Anggaran perbelanjaan langsung CPA bagi setiap pesakit setiap tahun adalah antara USD 169.03 dan USD 123,833.87. Komponen utama perbelanjaan langsung daripada poket ialah kos ubat (53.75%–98.97%). Semasa fasa prospektif, 244 pesakit telah dikaji. Pesakit dengan CPA mengalami kemerosotan status kesihatan yang ketara pada peringkat awal. Secara keseluruhan, 216 pesakit telah menyelesaikan 12 bulan terapi

antikulat. Selepas rawatan dengan itraconazole (57.3%) dan voriconazole (42.6%), 74.5% didapati peningkatan kesihatan yang ketara dengan pengurangan min skor 5 selepas 12 bulan. HRQoL meningkat daripada 58/100 (nilai dasar) kepada 55/100 (3 bulan), 54/100 (6 bulan), 54/100 (9 bulan) dan 53/100 (12 bulan). Peningkatan klinikal diperhatikan dalam 130 (60.18%) pesakit, penambahbaikan radiografi dalam 129 (59.72%), dan penambahbaikan mikrobiologi dalam 134 (62.03%) pesakit. Kajian semasa menunjukkan itraconazole dan voriconazole adalah sederhana berkesan untuk CPA, terutamanya jika diberikan selama 12 bulan. Pengenalpastian awal pesakit yang berisiko tinggi akan mempunyai kelebihan yang lebih jelas dalam menyediakan rawatan yang sesuai dan pengurusan unit rawatan rapi. Terdapat keperluan untuk penyelidikan yang lebih menyeluruh di fasiliti- fasiliti yang berkaitan bagi tempoh susulan yang lebih lama untuk mengesahkan penemuan penyelidikan ini.

PREVALENCE, CLINICAL MANIFESTATIONS, TREATMENT OUTCOMES, COST OF TREATMENT AND HEALTH RELATED QUALITY OF LIFE (HRQoL) OF CHRONIC PULMONARY ASPERGILLOSIS (CPA) IN A TERTIARY REFERRAL HOSPITAL IN LAHORE, PAKISTAN

ABSTRACT

Chronic Pulmonary Aspergillosis is a chronic progressive infection that destroys lung tissue in non-immunocompromised patients. There has been a dearth of investigation on the CPA. Therefore, a two-phase retrospective and prospective study was conducted to assess the epidemiology, clinical manifestations, treatment outcomes, risk factors associated with the development, prolonged Length of Stay, mortality, direct cost of treatment, and Health Related Quality of Life of CPA patients attending Gulab Devi Chest Hospital, Lahore, Pakistan. During retrospective phase (2017-2019), a total of 44,028 respiratory patients were reviewed. CPA was observed in 248 (0.56 %) cases. The prevalence of CPA was 563/100,000. A total of 218 CPA patients were included in this phase. The most common phenotype of CPA was Simple Aspergilloma (56.0%) followed by Chronic Cavitary Pulmonary Aspergillosis (31.2%) and Sub Acute Invasive Aspergillosis (12.8%) respectively. The most common symptoms in the CPA patients were cough (95.0%), fatigue (92.7%), sputum production (90.4%), fever (85.8%), hemoptysis (59.6%), and weight loss (34.9%). Tuberculosis (62.8%), Non-Tuberculosis Mycobacteria (30.7%), and Diabetes Mellitus (29.8%) were the most common underlying diseases. After CPA was diagnosed, all patients were treated with oral itraconazole (n = 152, 69.7%), voriconazole (n = 15, 6.98%), and amphotericin B (n = 51, 23.4%). Clinical

Improvement was observed in 122 (56.0%) patients whereas radiological and microbiological improvement was seen in 115 (52.7%) and 163 (74.7%) patients, respectively. The overall mortality rate was 27.1%. Multivariate regression analysis demonstrated old age (OR: 2.53), male gender (OR: 3.40), low BMI (OR:0.52), active TB (OR: 0.87), previous TB (OR: 1.36), smoking history (OR: 2.64), COPD (OR: 5.31), DM (0.30), Interstitial Lung Disease (OR: 4.08) and use of steroids (OR:1.96) as independent predictors of CPA. Six variables including smoking history (OR: 0.97), CCPA (OR: 0.84), previous TB (OR: 0.35), COPD (OR: 0.89), DM (OR: 4.23), and, hematological malignancies (OR: 0.08) were associated with the prolonged hospital stay. Eleven independent factors associated with mortality were age (OR: 0.17), CCPA phenotype (OR: 0.25), use of steroids (OR: 0.65), HRF (OR: 5.68), consolidation (OR: 17.08), pleural thickening (OR: 8.31), fungal ball (OR: 0.04), DM (OR: 2.34), previous TB (OR: 3.07), active TB (OR: 0.06), and HM (OR: 0.08). The range of direct out-of-pocket expenditure of CPA per patient annually was between USD 169.03 and USD 123,833.87. During prospective phase, 244 patients were studied. Overall, 216 patients completed 12 months of antifungal therapy. After treatment with itraconazole (57.3%) and voriconazole (42.6%), 74.5% patients gained significant health improvement with a mean reduction of score of 5 after 12 months. Clinical, radiological and microbiological improvements were observed in 130 (60.18%), 129 (59.72%) and 134 (62.03%), patients respectively. The current study demonstrated itraconazole and voriconazole are modestly effective for CPA, especially if given for 12 months. CPA treatment expenses burdens the patients as well as health care system, There is a need for appropriately powered multi-center trials with longer follow-up periods to validate the research findings.

CHAPTER 1

INTRODUCTION

1.1 Introduction

A common fungus called *Aspergillus* produces a wide range of clinical symptoms. Although inhaling *Aspergillus* conidia is a widespread method of exposure, only a small percentage of people exposed may get lung disease. Although there is growing understanding of the significance of genetics, the clinical characteristics, course, and prognosis of *Aspergillus* infections essentially depend on the degree of immune weakness of the host. Which clinical condition is more likely to arise depends on how the pathogen interacts with host immunological malfunction or hyperactivity (Kosmidis & Denning, 2015). Inhaling *Aspergillus* spores from soil or rotting vegetation is a common occurrence. These spores seldom induce infection in an immunocompetent host, although lung infection can occur in patients with neutropenia or severe immunosuppression. The skin, eyes, liver, kidneys, bone, and brain are some of the organs that might be affected by bloodstream dissemination (Mian et al., 2021). More than 180 species of *Aspergillus* make up this vast genus of common toxins, and a quarter of them are often found from people and other animals. Emericella, Eurotium, Fennellia, Hemicarpenteles, Neopetromyces, Neosartorya, and Petromyces are a few teleomorph (sexual states) taxa in the Ascomycota phylum that are related to the majority of clinically significant *Aspergillus* species. Diseases brought on by fungi of the genus *Aspergillus* are referred to as aspergillosis (Alcazar-Fuoli et al., 2008). Life-threatening infections in patients with impaired immune systems have increasingly been linked to *Aspergillus* species. This could range from minor local illnesses to deadly widespread infections. An allergic reaction to spores breathed may potentially

cause the disease. Most cases of pulmonary aspergillosis are caused by *Aspergillus fumigatus*, which is followed by *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus nidulans* (Summerbell & animals, 2003). Allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), and invasive pulmonary aspergillosis (IPA) are the three main phenotypes of pulmonary aspergillosis (Fig. 1). The category that develops mostly depends on the underlying characteristics of the host and how the fungus and the host interact (Kosmidis & Denning, 2015). The overlap between these categories is becoming more evident as chemotherapeutic and immunosuppressive drugs are used so frequently (Li, Jiang, & Shao, 2018).

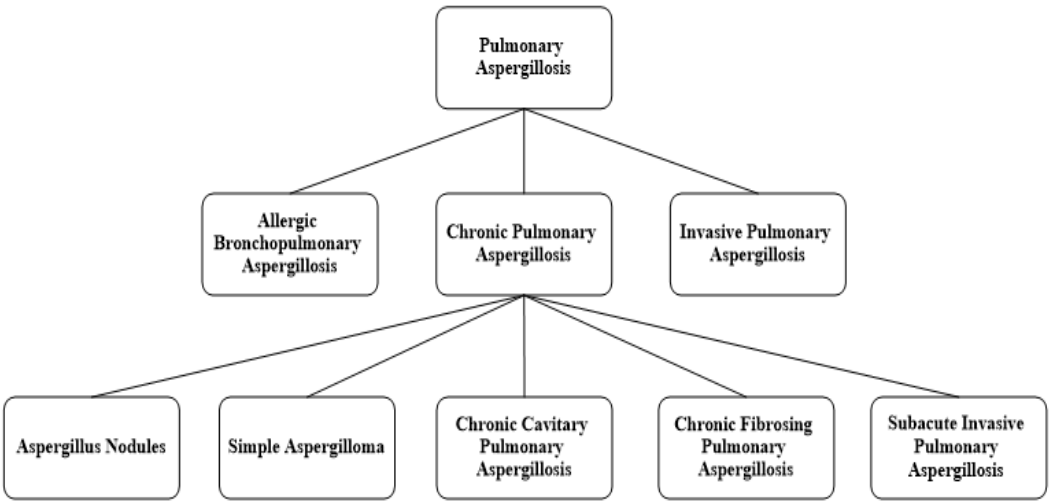


Figure 1.1 Phenotypes of Pulmonary Aspergillosis

(Kosmidis & Denning, 2015)

There are several known manifestations of CPA, including chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), and subacute invasive pulmonary aspergillosis (SAIA) [which may also be referred to as chronic necrotizing pulmonary aspergillosis (CNPA)]. When immune function is compromised to some extent, subacute IPA might manifest as nodules, consolidation,

or cavitation on chest imaging, as well as a more quickly progressing clinical course. CFPA has this appearance with the added features of pulmonary fibrosis, which may be progressive and destructive, while CCPA has this appearance with single or many cavities, with or without aspergilloma (s) (Muldoon et al., 2016c).

1.2 Chronic Pulmonary Aspergillosis

In Edinburgh, United Kingdom, chronic pulmonary aspergillosis (CPA) was initially identified as a deadly illness in 1842. Amphotericin was first administered to a patient for CPA-complicating tuberculosis in 1957. The term "mega-mycetome Intra-bronchiectasique" was used to characterise the first radiological description of an aspergilloma, which was made in France in 1938 (Denning et al., 2018b). Many clinical descriptions of aspergilloma were published in the middle of the 20th century. When aspergillosis was originally "classified" in 1959, the term "mycetoma" was used, although today this is used to describe a subcutaneous fungal infection. The discovery of *Aspergillus* antibody detection in London, UK, in the 1960s led to its widespread use as a method of establishing the cause of fungal balls seen on chest radiographs and tomography. Early in the 1980s, the terms semi-invasive pulmonary aspergillosis and chronic necrotizing pulmonary aspergillosis were developed (Muldoon et al., 2016c).

CPA was defined as non-immunocompromised patients who had at least one pulmonary cavity on thoracic imaging, positive anti-*Aspergillus* immunoglobulin G antibodies (precipitins) in blood, cultures, or biopsy implicating Aspergillus spp., and either symptoms (typically weight loss, fatigue, cough, hemoptysis, and breathlessness) for 3 months, with slowly progressing lung destruction with or without one or more fungal balls (simple aspergillomas) (Akram et al., 2021b; Denning et al., 2018b; Smith & Denning, 2011).

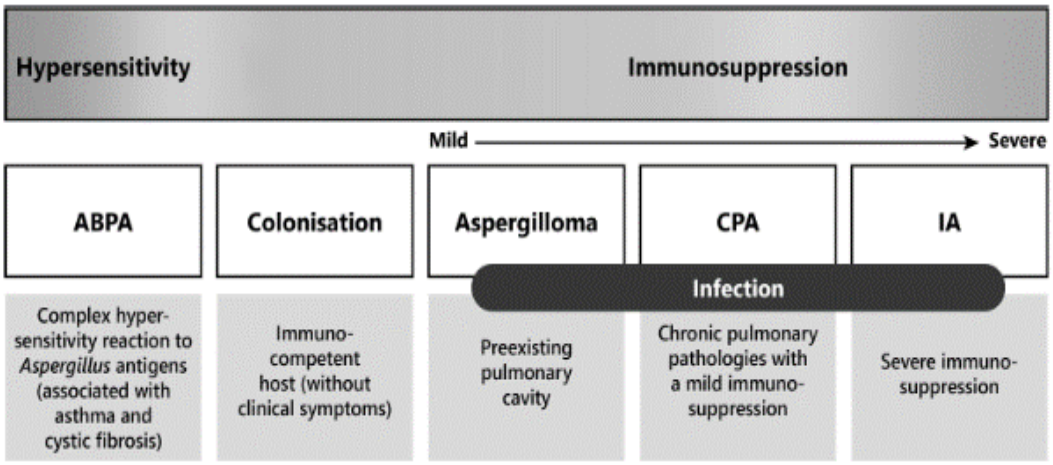
CPA is a distinctive fungal infectious disease with significant public health consequences. Globally, CPA is estimated to have an impact on more than 3 million people. PTB (pulmonary tuberculosis) cases that have already been treated are thought to account for over 1.2 million cases, whereas sarcoidosis patients are thought to be responsible for about 70,000 cases (Muldoon et al., 2016c; Prattes et al., 2019). As a result, PTB and emphysema are the main risk factors for CPA, and CPA seems to be more common in areas with high PTB prevalence. Additionally, the coexistence of CPA and PTB could make clinical distinction challenging. This patient category is frequently misdiagnosed and treated as smear-negative PTB on the basis of clinical symptoms and suggestive radiography (Benjelloun et al., 2015; Bongomin et al., 2017). CPA is most common among middle-aged and elderly adults, men, and those with a low BMI, suggesting that these features may be additional risk factors for developing the condition (Camara et al., 2015a; Denning et al., 2011a; Jhun et al., 2013a; Smith & Denning, 2011).

1.2.1 Causative agent

Aspergillus was regarded as one of the earliest genera of fungi in 1729 by Roman Catholic theologian and biologist Pier Antonio Micheli. There are currently around 330 different species of *Aspergillus*. The most clinically significant species are *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus terreus*, and *Aspergillus nidulans,* which are among the approximately 50 species that are known to be potentially harmful to humans. A general term known as aspergillosis is used to refer to essentially all infections caused by opportunistic fungus of the genus *Aspergillus* (Bongomin et al., 2020).

1.2.2 Pathogenesis

CPA is a chronic respiratory disease that primarily affects persons who have or have had lung lesions, such as cavities. The radiological manifestations of CPA include one or more cavities, with or without a fungal ball, or nodules progressing to lung parenchymal or pleural fibrosis. Particularly in patients with cavitary lung diseases, the pathogenesis of CPA is quite well understood (Pasqualotto, 2010; Roberts et al., 1987). Repeated exposure to A. fumigatus conidia, the most common causative agent of CPA, is unavoidable. The conidia's small diameter (3-5 m) makes it easier for them to enter alveolar gaps, where they cause saprophytic colonisation of lung cavities (Kosmidis & Denning, 2015; Kwon-Chung & Sugui, 2013). Aspergilloma present or absent (a complex aggregation of fungal mycelia, fibrin, mucus, inflammatory cells, and tissue debris), this can result in local inflammation, pleural and/or parenchymal fibrosis, the growth of new cavities or the expansion of the colonised cavity. When fungus develops inside a lung cavity and splits from the cavity wall, fungus balls are produced. The importance of genetic anomalies and immunological dysregulation in the occurrence and progression of CPA is still being studied (Bongomin et al., 2020; Harrison et al., 2012; Muldoon et al., 2016a). Diagram 1.2 highlights the many diseases brought on by *Aspergillus* species as a result of defective conidial clearance through mucociliary clearance or conidial phagocytosis by macrophages after inhalation. The severity of pulmonary aspergillosis can vary depending on the host's immune system, from a mild allergic reaction (hypersensitivity) to a potentially fatal invasive infection (severe immunosuppression).



Abbreviations: ABPA: Allergic Bronchopulmonary Aspergillosis, CPA: Chronic Pulmonary Aspergillosis, IA: Invasive Aspergillosis

Figure 1.2 Pathogenesis and Disease Spectrum of Pulmonary Aspergillosis (Kosmidis & Denning, 2015)

1.2.3 Clinical Manifestations

Patients who are not immunosuppressed in their middle age are more susceptible to CPA. It progresses slowly and may continue for years (Camuset et al., 2007a; Godet et al., 2014). The majority of CPA patients have clinical signs and symptoms, though some are asymptomatic and solely have radiological progression. Hemoptysis/hemosputum is the most recognisable and concerning symptom. Hemoptysis occurs in 12% to 43% of CPA patients (Farid et al., 2013; Jhun et al., 2013a; Salzer et al., 2017) and varies from blood streaking in sputum to massive and fatal hemoptysis. Patients with TB may experience hemoptysis, but this is typically merely a mild staining of the sputum with blood. Mild but persistent chest pain, discomfort, or tightness is another defining symptom that up to 37% of patients report (Sehgal et al., 2020). Fatigue and weight loss are other frequent but not universal symptoms. Dyspnea and productive cough are not enough to distinguish CPA from

other respiratory illnesses, such as pulmonary TB. When present, fever or pyrexia may point to a different or additional diagnosis, such as subacute invasive aspergillosis, in CPA patients. There have been reports of sweating both during the day and at night (Akram et al., 2021b; Denning et al., 2018b).

1.2.4 Risk Factors

The three conditions that are most frequently linked to the onset of CPA are TB, atypical Mycobacterium infections, along with COPD and emphysema. Recent studies that reflect the rise in TB epidemics show that the TB occurs more frequently than atypical Mycobacterium infections, COPD and emphysema in the development of CPA (Akram et al., 2021; Smith & Denning, 2011). Other disorders include silicosis, stage III or IV fibrocystic pulmonary sarcoidosis, and lung cancer (Camuset et al., 2007c; Smith & Denning, 2011). Sometimes the pre-existing cavity is the only factor contributing to the development of a CPA. In some cases, it is common to find a number of comorbidities (which constitute a so-called "mild immunosuppression"), such as alcoholism, tobacco usage, diabetes, glucocorticoid therapy, or TNF-inhibitor therapy. The most frequent condition that comes before CPA is pulmonary TB in many nations. Infection with pulmonary mycobacteria is the most frequent differential diagnosis of CPA (Denning et al., 2003b).

1.3 Prevalence and burden of Chronic Pulmonary Aspergillosis

In recent years, it has become widely accepted that the level of host immunity plays a significant role in determining the severity and origin of pulmonary aspergillosis. As of now, invasive bronchial aspergillosis, CPA, and allergic bronchopulmonary aspergillosis (ABPA) are the three phenotypes of pulmonary

aspergillosis that are recognized (Pena et al., 2011). There is a significant overlap in the diseases represented by these phenotypes, which are regarded to reflect a continuum of sickness. Although neutropenia is still the predominant risk factor for acute invasive aspergillosis (IA), individuals with prior pulmonary disease, particularly when it results in poor pulmonary clearance, are more likely to develop CPA (Soubani et al., 2011). Patients with CPA frequently have a variety of underlying pulmonary diseases, such as a history of tuberculosis, an active atypical mycobacterial infection, chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF), ABPA (a condition complicating, for example, asthma and CF), a prior pneumothorax, treated lung cancer, sarcoidosis, pneumoconiosis, emphysema and thoracic surgery. Corticosteroid use, alcoholism, diabetes mellitus, and immunosuppressive therapy are all examples of minor immunosuppression in CPA (Knutsen, Slavin, & Immunology, 2011). Idiopathic pulmonary fibrosis and ankylosing spondylitis are two situations where the symptoms of CPA help diagnose the underlying respiratory or immunological dysfunction (Calvet et al., 2010). As CPA frequently develops in cavities that have already formed, it might exacerbate other illnesses that result in lung damage, such as radiation therapy and cryptococcosis, respectively. Additionally, it has been observed that chronic hypersensitivity pneumonitis and aspergilloma are related (Schweer et al., 2014).

According to the risk factors, middle-aged patients are most commonly afflicted by CPA, but younger adults, such as those with a history of tuberculosis or CF, may also be infected. (Amin et al., 2010). Although *Aspergillus fumigatus* infection accounts for the majority of cases of CPA, *Aspergillus niger* and *Aspergillus flavus* also cause it occasionally. Rare Aspergillus spp. infections are an exception (Calvet et al., 2010; Giménez et al.).

1.3.1 Global burden of Chronic Pulmonary Aspergillosis

An uncommon or rare lung disease called CPA can make other respiratory conditions like sarcoidosis, COPD, or tuberculosis worse. Around 3 million individuals are considered to be affected by CPA worldwide, and if left untreated, 80% of CPA patients will die within 5 years (Kosmidis & Denning, 2015).

To date, 43 nations, including India, representing 45% of the world's population, have reported the annual incidence of CPA following TB and the 5-year prevalence of CPA. The countries with the highest reported CPA burdens are India (209,147), Nigeria (120,753), the Philippines (77,172), Pakistan (72,438), and Vietnam (55,509); the countries with the lowest reported CPA burdens are Jamaica (82), Trinidad and Tobago (110), Qatar (176), and Ireland (196). Asia had significantly higher burdens than any other continent (Bongomin et al., 2017; Denning, et al., 2011a) (Figure 1.3).

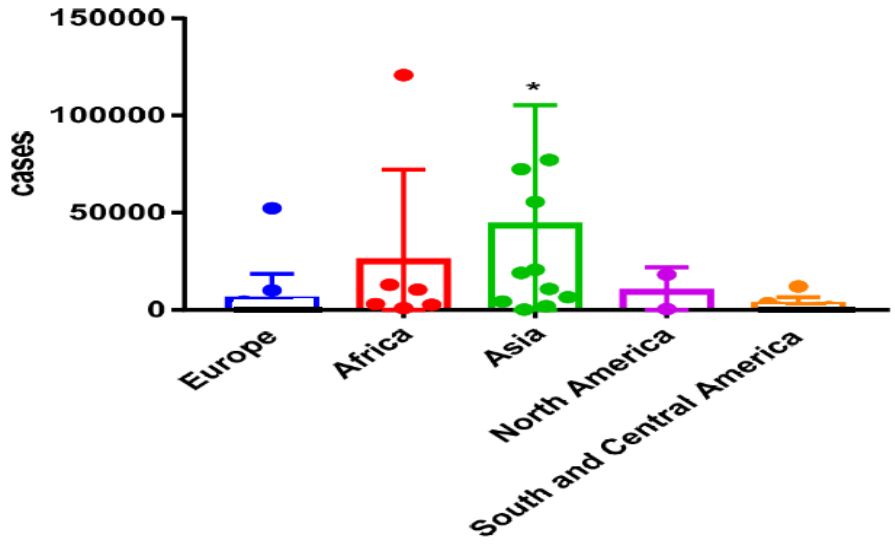


Figure 1.3 CPA Prevalence Across Continents

(Cadranel, et al., 2012)

There were 22 cases per 100,000 people across all of the reviewed nations with the lowest incidence in Canada (1.38 cases per 100,000), Algeria (2.2 cases per 100,000), Israel (2.5 cases per 100,000) and Germany (2.9 cases per 100,000); the highest incidence was estimated in Russia (126.9 cases per 100,000) followed by Philippines and Nigeria (78 cases per 100,000), Pakistan (70 cases per 100,000) and Vietnam (61 cases per 100,000) (Khwakhali & Denning, 2015; Oladele & Denning, 2014; Ruhnkeet al., 2014).

A preliminary estimate of the prevalence of CPA as a 5-year complication of pulmonary tuberculosis (1.17 million patients), ABPA (345 000 patients), and sarcoidosis (71 900 patients). Unfortunately, there are no statistics on people with COPD who have CPA complications, despite this being one of the largest patient subgroups (Denning et al., 2011b; Schweer et al., 2014).

1.3.2 Chronic Pulmonary Aspergillosis Burden in Pakistan

The most prevalent form of aspergillosis in Pakistan is chronic pulmonary aspergillosis (CPA). According to estimates, CPA is a major burden on the country as a result of TB. A recent study in Pakistan estimated that post-TB patients had a 15% prevalence of CPA (Zubair et al., 2021). The use of *Aspergillus*-specific IgG was recommended as the most beneficial test in CPA guidelines for usage in low- and middle-income countries. Although there are a variety of commercially accessible assays for the identification of *Aspergillus*-specific IgG, studies from Uganda and Europe reveal significant variability in cut-offs for positive, suggesting regional and genetic variances. Due to the high TB burden and the low number of cases unrelated to TB (i.e. due to sarcoidosis), chronic pulmonary aspergillosis (CPA) prevalence is also anticipated to be high (39/100,000) (Denning et al., 2011b). Immunocompetent

people with lung cavitary or non-cavitary disease develop CPA (Karim et al., 1997). CPA is more likely to occur in those who have had pulmonary tuberculosis, sarcoidosis, ABPA, chronic obstructive pulmonary disease (COPD), or pneumothorax. Pakistan has been projected to have a high burden of CPA, similar to other nations with high TB burdens. Since many centres lack the tests to identify *Aspergillus*-specific IgG and IgE, which are essential for the diagnosis of CPA and ABPA, it is very challenging to diagnose CPA in Pakistan. In smear-negative patients with suspected TB, it is difficult to eliminate CPA due to the lack of these diagnostics (Jabeen et al., 2020; Iqbal et al., 2017).

1.3.3 Prognosis and Outcomes of the Disease

The considerable morbidity that affects around 3 million individuals worldwide and the total 5-year mortality of up to 80%, which equates to an estimated 450,000 annual fatalities, pose challenges for CPA patients. Survival was 86%, 62%, and 47%, respectively, at 1, 5, and 10 years, in a cohort of 387 CPA patients referred to the UK's National Aspergillosis Centre from 1992 to June 2012 (Bongomin et al., 2018). One way to judge how well CPA is progressing is by follow-up imaging. CT and a chest radiograph both provide supplementary data. Follow-up CT is best performed using reduced-dose CT, which minimises radiation dose in accordance with the ALARA principle (As Low As Reasonably Achievable) (Hafeez et al., 2000; Hendee & Edwards, 1986). Follow-up imaging, is recommended every 3–6 months after beginning antifungal treatment (Cadranel, et al., 2012b) and then less often, or with any major change of clinical status (SoR B and QoE III). On CT scans or chest radiographs, virtually little change is seen in three months or less due to the slow nature of radiological change. Reduced pleural thickening, less material or fluid in a cavity,

a smoother internal cavity wall, and a smaller nodule or area of pericavitary consolidation are all indications of improvement. The development of an aspergilloma, new or merging cavities, a growing cavity, new cavities, or greater consolidation close to a cavity are all signs of failure (Felton et al., 2010). Key evaluations of therapy effectiveness involve comparing exactly identical anatomical lesions to determine the degree of consolidation, cavity wall thickness and size, fungal ball(s), and pleural thickening. It is also possible to use software to quantify the lesions' volume (Muldoon et al., 2016).

1.4 Health-related Quality of Life (HRQoL)

A better understanding of the disease burden is necessary given CPA's rising prevalence and chronicity, not only in terms of mortality but also in terms of morbidity and health-related quality of life to provide other crucial health indices, particularly when deaths do not occur right away after infection (Yeung et al., 2016). The development of numerous techniques and tools for evaluating the effectiveness of various aspects of health care, from comparisons of organizational and financing strategies to the evaluation of the cost-effectiveness of treatment options for specific patient groups to head-to-head comparisons of different drugs for the same condition, is the result of outcomes research's rapid evolution over the past ten years (Lambert et al., 1998; Ware et al., 1986). Tools created to measure health-related quality of life are some of the most significant tools created in recent years within the area of outcomes research (HRQOL). As a way to assess the worth of pharmacological therapy, the results from such instruments are increasingly used in addition to safety data, survival rates, and conventional clinical efficacy indicators. Additionally, regulatory agencies

are increasingly advocating the use of HRQOL outcomes in clinical trials (Beitz et al., 1996).

There is no one single gold standard for determining HRQoL; therefore, researchers must use tools that are appropriate for their intended research. Responsiveness is a crucial assessment attribute if the outcome of interest is the change in HRQoL, as it is in the evaluation of therapies (Apolone et al., 2001). The term responsiveness describes an instrument's capacity to identify changes in HRQL, regardless of how minor the changes may be. Clinical research findings could be interpreted incorrectly by investigators and physicians if the instruments are not responsive (Goldie et al., 1999). There are many validated HRQoL tools available for individuals with chronic lung illness, and choosing the best instrument is frequently difficult. The St. George Respiratory Questionnaire (SQRQ) and other disease-specific questionnaires are generally more sensitive than generic questionnaires like the Sickness Impact Profile or SF-36. Indeed, past research with CPA patients suggested that SGRQ was more responsive (Fine et al., 1999).

The St. George's Respiratory Questionnaire (SGRQ) is a respiratory-specific health-status measure that evaluates three domains: activity status, perception of the burden of respiratory illness on everyday living, and the most prevalent respiratory symptoms (Al-Shair et al., 2013). In addition to assessing the health state of people with COPD, asthma, idiopathic pulmonary fibrosis, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, and CPA, the questionnaire has also been well validated (Al-Shair et al., 2013a).

1.5 Cost of Treatment

The ageing of the population, advances in technology, and increased patient demands have put tremendous financial strain on healthcare budget holders and purchasers in recent years. These factors are compelling payers at all levels to take into account economic metrics including the cost-effectiveness and budgetary impact of healthcare interventions in addition to efficacy, safety, and quality (Fogel, 1997). The incidence of CPA has increased in recent decades (Pfaller & Diekema, 2010), as has the number of drug classes and agents used to combat these serious infections (Ashley, 2011; Mohr et al., 2008). When selecting an antifungal drug for a hospital's formulary, for the creation of a protocol for treatment or prevention, or for the treatment of a specific patient who is at risk for, has a suspected, or has a confirmed fungal infection, a number of variables should be taken into consideration. Identification of the fungus as a pathogen is one of these, along with treatment effectiveness, safety, tolerability, and cost. The relative cost of available therapies has grown in importance as a factor to be taken into account when choosing between agents due to growing concerns about the rising costs of healthcare and the lack of data demonstrating the superiority of one agent over another, particularly in regards to newer options (Johnson & Perfect, 2007). For disorders like CPA that require substantial healthcare resources to treat, economic strategies are especially crucial.

1.6 Problem Statement

About 56% of the world's population lives in developing countries, that are situated in tropical and subtropical regions of Asia, Africa, South, and Central America, where the temperature is hot and humid and suitable for fungi to grow. Below-optimum hospital care practice, A huge number of unskilled health workers

(quacks ((Who have not obtained formal medical education but practicing medical)), the overuse of steroids, intravenous drug addiction, and the availability of spurious medical care infusion sets are all possible risk factors for CPA in developing countries (Iqbal et al., 2016). The number of people at risk of CPA in developing countries is enormous. The incidence rates among at-risk patients fluctuate according to local epidemiology. Though the prevalence of the disease and the magnitude of the problem are thoroughly studied in the developed world, literature on the prevalence of CPA in developing countries is limited (Chakrabarti et al., 2011b; Gupta et al., 2000). The true prevalence of chronic Pulmonary Aspergillosis (CPA) is unknown in Punjab Pakistan.

The prevalence of these diseases, as well as healthcare resources, varies enormously among different countries. As a consequence, we often find important differences among published CPA cohorts, especially regarding predisposing conditions and prognosis. Globally, CPA after tuberculosis is the most common form, especially in countries with a high tuberculosis prevalence, while CPA complicating COPD or bronchiectasis is the most common form in countries with a lower tuberculosis prevalence and older populations (Benjelloun et al., 2015; Nam et al., 2010b; Smith & Denning, 2011). Given these variations, the study of local scenarios becomes important in our knowledge of CPA. Most CPA patients remain undiagnosed or misdiagnosed in Pakistan because of the lack of proper knowledge about the nature of the disease. To the best of our knowledge, no study analyzes a large patient cohort in Pakistan and describes the clinical symptoms and associated risk factors of CPA.

The cost of treatment is a major contributing factor to the completion of treatment in developing countries like Pakistan. No other study has evaluated the cost of treatment and most economical antifungal therapy in Pakistan.

It is generally acknowledged that people with chronic illnesses place a great importance on their whole welfare, including their emotional and social health in addition to their physical health. The health care provider can predict the things that will increase patient satisfaction by using HRQoL to provide them with information about the typical changes in morbidity at a specific period. As a result, measuring HRQoL has gained significance as a health outcome and has drawn the attention of researchers, legislators, and healthcare workers. The effect of CPA on patients' HRQoL has not been adequately addressed. There are surprisingly few studies that have examined CPA patients' HRQoL, according to a review of the literature. These studies conducted it either cross-sectionally or with smaller CPA subsamples (Jaber et al., 2016; Al-Shair et al., 2013; Oh et al., 2009). we do not come across any large-scale prospective study demonstrating the response of antifungal treatment, treatment outcomes, and Health-Related Quality of life (HRQoL) of CPA patients in Pakistan. Factors related to HRQoL need to be identified in this population to provide culturally sensitive interventions to improve the efficiency of management and to help these patients regain or maintain efficient control of their lives.

The current treatment guidelines recommend long-term oral azole medication, with frequent side effects or therapeutic failure necessitating a switch to a different azole or an injectable antifungal drug. Only a few studies evaluated the results of CPA treatment. The majority of these studies are brief and of a small size. There is no long term, prospective study that evaluated the CPA therapy outcomes in Pakistan.

1.7 Research Objectives

The current study's research objectives were divided into two phases based on the aforementioned problem description.

1.7.1 Retrospective Phase (Phase-I)

The specific objective of this phase is to determine the prevalence of CPA among patients attending a tertiary-level teaching hospital. To achieve a specific objective, the retrospective phase of the study includes the following objectives.

1. To Determine the clinical manifestation of chronic Pulmonary Aspergillosis (CPA) in tertiary care hospitals of Pakistan.
2. To determine the associated risk factors for developing Chronic Pulmonary Aspergillosis (CPA).
3. To Determine the risk factors associated with the prolonged length of stay (LOS) of Chronic Pulmonary Aspergillosis (CPA) in hospital.
4. To Evaluate the risk factors related to mortality of Chronic Pulmonary Aspergillosis (CPA) patients.
5. Evaluation of the treatment outcomes at the end of treatment (EOT) among CPA patients.
6. Determination of the direct out of pocket cost of treatment of Chronic Pulmonary Aspergillosis (CPA) in a tertiary care hospital.

1.7.2 Prospective Phase (Phase-II)

The specific objective of this phase is to assess the Health-Related Quality of life (HRQoL) of Chronic Pulmonary Aspergillosis (CPA) patients at various treatment stages, for which the following objectives were included in the prospective phase.

1. To measure and compare the Health-Related Quality of life (HRQoL) of Chronic Pulmonary Aspergillosis (CPA) patients at various treatment stages (Baseline, 3rd month, 6th month, 9th month, 12th month)

by using the validated and reliable St. George Respiratory Questionnaire (SGRQ).

2. To Determine of the treatment outcomes (Clinical, radiological and serological features) in Chronic Pulmonary Aspergillosis (CPA) patients treated in tertiary care hospitals.

CHAPTER 2

LITERATURE REVIEW

Environmental exposure to Aspergillus spp. and their conidia is frequent. However, only a small percentage of individuals have clinical illness, and the course of the illness is frequently influenced by the host immunological status, genetic predisposition, underlying lung pathology, and previous pulmonary infections like tuberculosis (TB) (Soubani & Chandrasekar, 2002).

In immunocompetent patients, chronic pulmonary aspergillosis (CPA) frequently develops as a saprophytic infection in a pre-existing cavity after an infection like tuberculosis (TB) or prior lung surgery (Muldoon et al., 2016). The main characteristics of CPA are fibrosis, pleural thickening, and gradual deterioration of lung tissue with increasing cavity formation. Patients with lung cavitation diseases or structural pulmonary anomalies are most likely to develop the condition (Bongomin et al., 2018). The prevalence, clinical symptoms, risk factors, quality of life, and treatment outcomes of CPA have been the subject of several studies conducted around the globe in the past.

2.1 Main focus of literature review

The prime focus of the literature review was to ascertain

- The clinical manifestations of CPA patients.
- The Prevalence of CPA.
- Associated risk factors for developing CPA, prolonged length of stay, and mortality.
- Health-related quality of life of CPA patients.

- Cost of treatment of CPA.
- Treatment outcomes of CPA.

An in-depth literature review was conducted. All the objectives of the current study were separately searched in the previously available literature.

2.2 Study Eligibility and Search Strategies

The literature evaluation covered all types of clinical research examining the clinical characteristics and epidemiology of chronic pulmonary aspergillosis (CPA), including retrospective, prospective, case-controlled series, case reports, and clinical trials. Thus, the review of the literature is divided into two sections: chronic pulmonary aspergillosis (CPA) infection and associated health-related quality of life (HRQoL). We searched PubMed/MEDLINE, Google Scholar, Science Direct, EMBASE, WHO CPA bulletin, Cochrane Library, and Higher Education Commission's digital library for the following terms: chronic Pulmonary Aspergillosis (CPA), CPA and its causative agent, CPA and its diagnosis, CPA and fungal ball, CPA and mycobacterial infection, CPA and nontuberculous mycobacteria (NTM), CPA and allergy bronchopulmonary aspergillosis, CPA and aspergilloma, CPA and *Aspergillus nodule*, CPA and chronic cavity pulmonary aspergillosis, CPA and subacute invasion pulmonary aspergillosis, CPA and invasive aspergillosis, CPA and its global burden, CPA and its treatment, CPA in Pakistan, CPA induced complications, complications of CPA, and CPA and Health-Related Quality of Life (HRQoL).

2.3 Classification of Chronic Pulmonary Aspergillosis

Chronic pulmonary aspergillosis is distinguished by scarring (fibrosis) in the lungs as well as a progressive loss of lung tissue, which leads to the formation of empty

spaces (cavitation) as well as the widening and extension of already existing spaces (expansion). The membranes surrounding the lungs have thickened as well (pleural thickening). Several different disease patterns are included by the phrase "chronic pulmonary aspergillosis," including:

- Aspergilloma
- Aspergillus nodule
- Chronic cavitary pulmonary aspergillosis
- Chronic fibrosing pulmonary aspergillosis
- Subacute invasive pulmonary aspergillosis

Chronic pulmonary aspergillosis can recur after treatment (Muldoon et al., 2016c).

2.3.1 Aspergilloma

The growth of a fungus ball called an aspergilloma is the most recognizable symptom of aspergillosis. These growths are a tangled mass of inflammatory cells, mucous, tissue fragments, fungal fibers, and blood clotting protein (fibrin) (Camuset et al., 2007). Aspergillomas develop in air sacs or cavities in the lungs that may have developed as a result of prior lung illness (e.g., tuberculosis or emphysema). Most affected people (asymptomatic) undergo years without showing any overt symptoms. The most common symptoms are wheezing, shortness of breath, chest pain, exhaustion, a persistent cough that produces blood (hemoptysis), and unintentional weight loss (Pena et al., 2011). The size of an aspergilloma may not change, but it may diminish or disappear on its own. If an aspergilloma damages neighboring lung tissue

over time, it may eventually get larger; this condition is known as chronic cavitary pulmonary aspergillosis (Regnard et al., 2000).

2.3.2 Aspergillus Nodule

A little mass of infected tissue is called an Aspergillus nodule. These nodules can develop in people with healthy immune systems (immunocompetent hosts). Affected people may acquire a single nodule or several nodules, frequently without the development of empty spaces (cavitation). Many people don't show any symptoms (asymptomatic), but other people get a cough, a chest infection, or their lung condition, like asthma or chronic pulmonary obstructive disease, gets worse (Pisa et al., 2016).

2.3.3 Chronic Cavitary Pulmonary Aspergillosis

People who have this phenotype of aspergillosis may suffer the formation of new cavities or empty spaces in the lungs (cavitation) or the widening or extension of already existing cavities (expansion). An x-ray or CT scan of these people reveals that almost half of them have aspergillomas. They can lose weight unintentionally, develop a persistent cough that generates mucus, cough up blood, feel exhausted, and have shortness of breath. Fever or nocturnal sweats can happen less frequently. Occasionally, there can be substantial and widespread scarring (fibrosis) (Sehgal et al., 2020).

2.3.4 Subacute Invasive Pulmonary Aspergillosis

Subacute Invasive Pulmonary Aspergillosis (Chronic Necrotizing Aspergillosis). This phenotype of aspergillosis, also known as semi-invasive aspergillosis, shares many characteristics with chronic cavitary pulmonary aspergillosis but develops more

rapidly, typically over a period of one to three months. This is because it mostly affects people who have some degree of immunosuppression (e.g. people taking high doses of steroids) (Bongomin et al., 2018). Invasive aspergillosis is typically more rapidly fatal in patients with more severe immunosuppression (caused, for example, by chemotherapy or organ transplantation). Contrary to invasive aspergillosis, subacute invasive pulmonary aspergillosis manifests as a long-lasting, gradually progressing condition that does not affect the blood vessels or other organ systems (angioinvasion). An aspergilloma (fungal ball) may form in a cavity caused by the initial infection's loss of lung tissue in certain affected people. General symptoms associated with this form of aspergillosis include fever, night sweats, a cough that brings up sputum, fatigue, a general feeling of poor health (malaise), and unintended weight loss. Affected individuals may also cough up blood or sputum; this can vary from mild to severe (Sehgal et al., 2020).

2.4 Studies reporting prevalence/incidence of Chronic Pulmonary Aspergillosis

Several studies reported prevalence and incidence of CPA at global and regional levels.

2.4.1 Global burden of Chronic Pulmonary Aspergillosis

The literature search identified only three retrospective studies from all over the globe reporting the prevalence/incidence of CPA in specific respiratory diseases or conditions (Table 2.1).

Although it is difficult to estimate the prevalence and incidence of CPA, the disease's worldwide burden is growing (Denning et al., 2011b, 2013b). The prevalence

of CPA has been estimated at 3,000,000 cases worldwide (Brown et al., 2012). According to an analysis of data from 43 nations in 2017, Russia had the greatest incidence (126.9 cases per 100,000), followed by the Philippines, Nigeria (78 cases per 100,000), Pakistan (70 cases per 100,000), and Vietnam (61 cases per 100,000). The incidence was 22 cases/100,000 (14.2-30.59, 95% CI) for all the study's participating nations (Al-Shair et al., 2013) with 5- and 10-year mortality rates as high as 38% and 53%, respectively, even when treated with antifungal therapy (Lowes et al., 2017).

Asthma of any severity may be complicated by allergic bronchopulmonary aspergillosis (ABPA) which may itself be complicated by chronic pulmonary aspergillosis (CPA) (Jewkes et al., 1983; Smith & Denning, 2011). The majority of ABPA patients experience recurrent lung infections, thick sputum plugs, and poorly managed asthma (often associated with bronchiectasis). CPA, unlike invasive aspergillosis, affects people who are not immune compromised, which is likely the case for the majority of ABPA patients (Denning, 2008).

One or more aspergillomas in an existing cavity exacerbate fibrocystic sarcoidosis in chronic pulmonary aspergillosis (CPA). If significant doses of corticosteroids are used, invasive aspergillosis may develop. Despite data from the National Aspergillosis Centre in Manchester, UK, indicating sarcoidosis in 7.1% of patients, many other diseases can be made worse by CPA. Other diseases include previous pulmonary tuberculosis, allergic bronchopulmonary aspergillosis (ABPA), pneumothorax, bullous lung disease, nontuberculous mycobacterial pulmonary infection, and chronic obstructive pulmonary disease (COPD) (Hours et al., 2008; Smith & Denning, 2011).