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ORIGINAL ARTICLE

Serious fungal infections in Pakistan

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Abstract The true burden of fungal infection in Pakistan is unknown. High-risk populations for fungal infections [tuberculosis (TB), diabetes, chronic respiratory diseases, asthma, cancer, transplant and human immunodeficiency virus (HIV) infection] are numerous. Here, we estimate the burden of fungal infections to highlight their public health significance. Whole and at-risk population estimates were obtained from the WHO (TB), BREATHE study (COPD), UNAIDS (HIV), GLOBOCAN (cancer) and Heartfile (diabetes). Published data from Pakistan reporting fungal infections rates in general and specific populations were reviewed and used when applicable. Estimates were made for the whole population or specific populations at risk, as previously described in the LIFE methodology. Of the 184,500,000 people in Pakistan, an estimated 3,280,549 (1.78%) are affected by a serious fungal infection, omitting all cutaneous infection, oral candidiasis and allergic fungal sinusitis, which we could not estimate. Compared with other countries, the rates of candidaemia (21/100,000) and mucormycosis (14/100,000) are estimated to be very high, and are based on data from India. Chronic pulmonary aspergillosis rates are estimated to be high (39/100,000) because of the high TB burden. Invasive aspergillosis was estimated to be around 5.9/100,000. Fungal keratitis is also problematic in Pakistan, with an estimated rate of 44/100,000. Pakistan probably has a high rate of certain life- or sight-threatening fungal infections.

Introduction

A tremendous burden of infectious diseases and non-communicable diseases (NCDs) exists in Pakistan [1, 2]. In the absence of a national healthcare system, very limited surveillance is done with regards to various infectious and non-infectious diseases. Fungal infections are no exceptions and the true burden of even a single fungal infection is unknown. Fungal infections have been recently identified as 'hidden killers' as mortality due to top ten invasive fungal infections (IFIs) have been estimated to be equivalent to tuberculosis (TB) and now significantly exceed malaria [3]. Laboratory- and institutional-based reports from the country highlight the existence of these infections in both community and nosocomial settings. High-risk populations for fungal infections [tuberculosis (TB), diabetes, chronic respiratory diseases, asthma and cancer] are prevalent in Pakistan [4–6]. The situation becomes more complicated with the poor fungal diagnostic capabilities of most laboratories in Pakistan, emergence of antifungal resistance, lack of antimicrobial stewardship, poor

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infection control practices and non-availability of essential antifungal agents.

In this study, we have estimated the burden of fungal infections in Pakistan to highlight the public health significance of these infections.

Methods

The resources used for population estimates and morbidity data of conditions at risk were determined by reviewing national and global data (Table 1) [7–34]. Published data from Pakistan reporting fungal infections rates in general and specific populations were reviewed and used when applicable (Table 1). Estimates were made for the whole population or specific populations at risk, as previously described in the LIFE methodology.

Results and discussion

Based on our data analysis, among the 184.5 million people in Pakistan, an estimated 3.28 million people (1.78%) yearly are affected by a serious fungal infection (Table 2). The gross domestic product of Pakistan was $1275 per capita in 2013.

Cryptococcal meningitis and *Pneumocystis* pneumonia

We estimated that, yearly, around 794 and 2200 cases of cryptococcal meningitis and *Pneumocystis* pneumonia (PCP), respectively, occur in human immunodeficiency virus (HIV)-infected patients in Pakistan.

Cryptococcal infections with variable clinical presentations have been reported in various immunocompromised patient populations from Pakistan [8, 9, 35]. Two studies in HIV patients from Pakistan have reported rates of 2.5 and 9%, respectively, for cryptococcal meningitis in their patients [8, 9]. Another study assessing culture-positive meningitis in cancer patients reported a rate of 1 in 40,000 cancer patients [11].

PCP in HIV patients from Pakistan has been reported to occur at a frequency of around 16% in two studies [8, 9]. Apart from HIV populations, its incidence in other patient populations has not been reported from Pakistan. A retrospective analysis of 30 cases of PCP from a tertiary care hospital has reported HIV infection as an underlying disorder in 30% of their patients [36]. It would not be reasonable to extrapolate this ratio to the whole of Pakistan, because of the selective nature of patients seen at this centre. There is a general lack of studies estimating PCP incidence in these specific populations.

Oesophageal candidiasis

The annual burden of oesophageal candidiasis is estimated to be around 3231 cases in HIV-infected patients. Oesophageal candidiasis is an opportunistic infection in patients with deficient cell-mediated immunity and is an acquired immune deficiency syndrome (AIDS)-defining illness. Variable rates of oesophageal candidiasis ranging from 14 to 33% have been reported in HIV patients from Pakistan [8, 9, 12]. This infection has also been reported in non-HIV patients in Pakistan with carcinoma, diabetes mellitus, chronic steroid use and broad-spectrum antibiotics as significant risk factors [37]. However, the true burden of oesophageal candidiasis could not be estimated in non-HIV patients.

Candidaemia

Based on data from India [14, 15], we estimated a high burden of candidaemia in our population. The case fatality rate ranges from 23 to 52% in reports from Karachi [38, 39] and 24% from a neonatal intensive care unit (ICU) [40]. If a 40% mortality rate is used, then an estimated 15,498 people die with candidaemia annually in Pakistan. Furthermore, candidaemia is only a subset of all patients with invasive candidiasis, as blood cultures are only about 38% sensitive [41, 42]. This situation becomes worse with increase in the isolation of fluconazole-resistant *Candida* species, including *Candida auris*, in the country [43].

Patients with upper gastro-intestinal disease and prolonged ICU stay have a higher proportion of intra-abdominal candidiasis compared to lower gastro-intestinal surgery patients with short stay who have moderate risk [44]. Extrapolating from the ICU admission rate of 1.6/100,000 into ICU beds reported from a regional country, Sri Lanka [45], and assuming that 50% of patients admitted to ICUs are for surgical reasons, the population at risk for intra-abdominal candidiasis is calculated to be 1480. Among surgical ICU patients, intra-abdominal candidiasis is about 10% in patients with moderate risk, which includes patients with upper gastro-intestinal surgery. This brings the burden of intra-abdominal candidiasis to 148. However, this may be an underestimate, as there are limited ICU beds and a large undetermined number of patients may end up remaining in general wards without intensive care.

Mucormycosis

Around 25,830 cases of mucormycosis were estimated from Pakistan using a prevalence of 0.14/1000 population

Table 1 Baseline population and prevalence of fungal infections

Disease	Baseline population	Assumption	Prevalence	Reference
Cryptococcal meningitis	HIV patients below CD4 cell count of 200 cells/μL Estimate: HIV patients in need of ART: 55,000	Number eligible for ARV divided by 2 to get the rough number <200 and then assuming that only 50% present for care in that year	2.5–9%	[7–9]
	All cancer patients			
	Estimate: 14,8041		0.0025%	[10, 11]
Pneumocystis pneumonia	HIV patients below CD4 cell count of 200 cells/μL Estimate: HIV patients in need of ART: 55,000	Number eligible for ARV divided by 2 to get the rough number <200 and then assuming that only 50% present for care in that year	16%	[7–9]
Oesophageal candidiasis	HIV patients below CD4 cell count of 200 cells/μL Estimate: HIV patients in need of ART: 55,000	Number eligible for ARV divided by 2 to get the rough number <200 and then assuming that only 50% present for care in that year	14–33%	[7–9, 12]
Candidaemia	General population Estimate: 184,500,000		21/100,000	[13–15]
Invasive aspergillosis	Chronic obstructive pulmonary disease Estimate: Adults >40 years old in Pakistan (20.4% of population) = 37,638,000	33% of COPD patients >40 years of age are admitted to hospital each year and 3.9% will develop invasive pulmonary aspergillosis	3.9%	[13, 16, 17]
	Estimate: COPD prevalence (2.1% of adults >40 years old) =790,398			
	33% get hospitalised =260,831 admissions			
	Lung cancer patients	2.6%	2.6%	[10, 18]
	Estimate: 6800 Myeloid leukaemia (2% of all cancers)	10% rate of IA in acute myeloid leukaemia (over the year, not per neutropaenic episode) + equal number for all other haematological conditions	10%	[19, 20]
	Estimate: 2961			
Mucormycosis	General population Estimate: 184,500,000		14/100,000	[13, 21]
Recurrent vaginal candidiasis (4×/year +)	Adult female between age 15–50 years old (50.6% of female population) Estimate: 47,024,000		6%	[13, 22]
Allergic bronchopulmonary aspergillosis	Adult asthmatic patients (61% of population are adults and of those 3.3% are asthmatic) Estimate: 3,707,897	2.5% of adult asthmatic patients in Pakistan will develop ABPA	2.5%	[13, 23, 24]
	Cystic fibrosis			
	Estimate: 18,450		9%	[13, 25, 26]
Severe asthma with fungal sensitisation	Adult patients with severe asthma (10% of adult asthmatics) Estimate: 370,790	35% of adult asthmatics will develop SAFS	35%	[13, 23, 24]
Chronic pulmonary aspergillosis	Pulmonary TB alive patients in 2014 (estimated by subtracting extrapulmonary cases and expired cases from total new cases) Estimate (2014): [308,417 − (57,463 + 48,100)] = 202,854 alive pulmonary TB patients with cavitary disease	35% (25–50%) of alive cases of pulmonary TB in 2014 will develop cavitary disease; of these, 22% will develop CPA	22%	[5, 27]

Table 1 (continued)

Disease	Baseline population	Assumption	Prevalence	Reference
	Estimate: 70,999			
	Pulmonary TB alive patients with non-cavitary disease Estimate: 131,855	65% (50%–75%) of alive cases of pulmonary TB in 2014 will develop non-cavitary disease; of these, 2% will develop CPA	2%	[27]
	Sarcoidosis Estimate: 8432	Incidence of sarcoidosis is 4.57/100,000 population; of these, 6% will develop CPA	6%	[13, 28, 29]
Fungal keratitis	Patients with infectious keratitis (0.148% of general population) Estimate: 273,060		8–51%	[13, 30–33]
Mycetoma	General population Estimate: 184,500,000		0.01–0.1/100,000	[13, 34]

and 38% mortality, as computed in India [21]. Recent data from developing countries indicate increasing trends in mucormycosis cases, including India [46]. Several reports from Pakistan also indicate mucormycosis as an infection in various patient groups [47–49]. High mortality rates despite aggressive surgical debridement and amphotericin B therapy have been reported; an attributable mortality rate of 38% leads to ~9815 patients expiring annually due to mucormycosis in Pakistan. Although infections have been reported in patients with no apparent risk factors [49], isolated renal mucormycosis has not yet been reported from Pakistan. Even if these cases (around 8% of our estimate) are removed from our estimation, the burden of mucormycosis is still substantial. In addition, the proportion of population at highest risk for mucormycosis, i.e. diabetics, is higher in Pakistan than in India: 10% [50] versus 8% of the general population, respectively [51].

Table 2 Estimated burden of fungal infections

	Total burden	Number of infections per underlying disorder per year					Rate/100,000
		None	HIV/AIDS	Respiratory	Cancer/Tx	ICU	
Cryptococcal meningitis	794	–	790[a] (344–1237)	–	4	–	0.4
Pneumocystis pneumonia	2200	–	2200	–	–	–	1.2
Oesophageal candidiasis	3231[a]	–	3231 (1925–4537)	–	–	–	1.7
Candidaemia	38,745	–	–	–	–	–	21
Intra-abdominal candidiasis	148	–	–	–	–	148	0.08
Invasive aspergillosis	10,949	–	–	–	777	10,172	5.9
Mucormycosis	25,830	–	–	–	–	–	14
Recurrent vaginal candidiasis (4×/year)	2,821,440	2,821,440	–	–	–	–	3036[d]
ABPA	94,358	–	–	92,697 + 1661[b]	–	–	51
SAFS	129,776	–	–	129776	–	–	70
Chronic pulmonary aspergillosis	72,438	–	–	71,932 + 506[c]	–	–	39
Fungal keratitis	80,553[a]	80,553[a] (21,845–139,260)	–	–	–	–	44
Mycetoma	92[a]	92[a] (18–185)	–	–	–	–	0.05
Total burden estimated	3,280,554						1778

[a] Mean incidence

[b] In patients with cystic fibrosis

[c] In patients with sarcoidosis

[c] Rate for female population only

Recurrent vulvovaginal candidiasis

It is estimated that, yearly, 2,821,440 women of reproductive age suffer from recurrent vulvovaginal candidiasis in Pakistan. Due to both over- and under-diagnosis and self-treatment with over-the-counter topical antifungal agents, population-based data regarding the frequency of recurrent vulvovaginitis in Pakistan is lacking. Our estimates in this study were determined using data by Foxman et al., who report recurrent vulvovaginitis in ~9% of unselected females based on internet questionnaires [22, 52]. We have used a 6% rate, as women are inclined to over-diagnose 'yeast' infection. A study conducted to estimate the burden of reproductive tract infection in urban women in Pakistan reports vaginal candidiasis as the second most common genital infection, with a prevalence of 7–12% [53].

Aspergillosis

We estimated a high burden of allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) in adult asthmatic patients in Pakistan, because asthma is relatively common (3.3% prevalence adapted from India) [23], with 10% of these developing severe asthma. Annually, around 94,358 adult asthmatic patients will develop ABPA and 129,776 will develop SAFS. Although ABPA has been reported in asthmatic children from India [54] and SAFS from the UK [55], we have not attempted to estimate the burden of these problems. *Aspergillus* species has been reported to be the most common environmental fungus from Southern Pakistan in both indoor and outdoor environments [56]. Higher indoor concentration of *Aspergillus* species in the indoor environment was also associated with acute asthma exacerbation [57]. ABPA, often misdiagnosed as TB, has been reported to occur in patients from Pakistan [58]. In one series, around 76% of ABPA cases occurred in asthmatic patients, followed by 17% of cases in patients with cystic fibrosis or non-cystic fibrosis bronchiectasis [59].

ABPA is known to occur in older children, teenagers and adults with cystic fibrosis. Cystic fibrosis is often underdiagnosed in the Pakistani population, as appropriate diagnostic tools are not available; therefore, accurate prevalence in the country is not known [60]. However, cystic fibrosis prevalence of 1 in 9000 population has been reported in South Asian Canadian immigrants, as well as World Health Organization (WHO) estimates suggesting a prevalence of 1 in 10,000–40,000 in the Asian population [25, 61]. Considering a prevalence of 1 in 10,000 population and as 9% of these will develop ABPA as suggested by a recent meta-analysis, we have estimated 1661 cases per year in Pakistan [26].

Chronic pulmonary aspergillosis (CPA) prevalence is also estimated to be high (39/100,000) because of the high TB burden, with only a few cases not related to TB (i.e. due to sarcoidosis). CPA occurs in immunocompetent individuals with prior or existing pulmonary cavitary or non-cavitary disease [62, 63]. Patients with prior pulmonary TB, sarcoidosis, ABPA, chronic obstructive pulmonary disease (COPD) and pneumothorax are particularly at risk of developing CPA. As seen in other high TB burden countries, a high burden of CPA has been estimated in Pakistan. In Pakistan, it is extremely difficult to diagnose CPA, as tests to detect *Aspergillus*-specific IgG and IgE, crucial for the diagnosis of CPA and ABPA, are not available in many centres. Non-availability of these tests makes it problematic to exclude CPA in smear-negative patients with suspected TB.

Invasive aspergillosis (IA) is mainly reported in immunocompromised individuals; however, in developing countries, including Pakistan, IA has been reported in hosts with no apparent immune defect [64]. Around 10,172 COPD patients develop IA annually in Pakistan (using the 3.9% rate in hospitalised patients from China, based on culture and imaging) [17]. Assuming that 2% of all cancers as reported in Karachi, Pakistan are myeloid leukaemia [19] and in these patients 10% will develop invasive pulmonary aspergillosis (IPA) [20], we estimated around 296 cases in this population. This is probably an underestimate, as other patients with haematological malignancies are also at risk of IPA; therefore, an equal number of cases was estimated for all other haematological conditions. In addition, we also estimated 177 cases of IPA per year in lung cancer patients. Emerging populations at risk of IPA are patients with pre-existing lung disease like COPD, critically ill patients in the ICU, especially those given corticosteroids, diabetes and advanced liver disease [64]. IA has been reported from Pakistan in patients with bone marrow, renal and liver transplant, and haematological malignancy [65–67]. A study conducted recently at our centre on 69 patients revealed diabetes and chronic renal failure as the most prominent risk factors for pulmonary aspergillosis. Prior or active TB was found in 50% of these patients. The overall mortality was 20%, with around 70% mortality in patients admitted to the ICU. Diabetes mellitus was identified as an independent risk factor for mortality [68].

Fungal keratitis

Various studies from the country report rates of fungal keratitis ranging from 8 to 51% amongst patients presenting with infectious keratitis [31–33]. Based on data from China [30], around 273,060 cases of microbial keratitis annually are estimated in Pakistan. A fungal aetiology is likely in 80,553 cases. Our estimated rates of fungal keratitis in Pakistan (Table 2) are approaching those of Nepal, where fungal keratitis has been

reported to be a common fungal infection, with a rate of 73/100,000 [69]. This rate is alarming and points toward a major need for improved diagnostics, enhanced management strategies and education.

Mycetoma

Using an incidence of 0.01–0.1/100,000 [34], around 92 cases of mycetoma occur annually in Pakistan. Around 40% of cases are fungal, with *Madurella mycetomatis* as the most common agent [34]. Apart from sporadic case reports that confirm the existence of disease in the country, no data regarding the burden of mycetoma are available from Pakistan. A study performed in Pakistan has reported that around 40% (5/12) of all cases of mycetoma in their centre was due to fungi [70]. Due to the paucity of exact data, a burden of only 18–185 cases per year seems to be an underestimate.

Conclusion

Fungal infections are common in Pakistan, but grossly underdiagnosed. Diseases of real concern are candidaemia (21/100,000) and invasive candidiasis, mucormycosis (14/100,000), which may exceed invasive aspergillosis, fungal keratitis (44/100,000) and fungal asthma (>100/100,000). Efforts to improve the diagnosis of these conditions, better understand their local epidemiology and institute preventative measures are called for.

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