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Serious fungal infections in Pakistan

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Abstract:**Introduction:**

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 HIV infection) are numerous. Here we estimate the burden of fungal infections to highlight their public health significance.

Methods:

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 was reviewed and used when applicable. Estimates were made in for the whole population, or specific populations at risk, as previously described in the LIFE methodology.

Results: Of the 1,845,000,00 people in Pakistan, an estimated 3,280,549 (1.78%) people 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.

Conclusions: 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 (NCD) exists in Pakistan (1, 2). In the absence of 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 (IFI) 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 (TB, diabetes, chronic respiratory diseases, asthma, and cancer) are prevalent in Pakistan (4, 5, 6). The situation becomes more complicated with poor fungal diagnostic capabilities of most laboratories in Pakistan, emergence of antifungal resistance, lack of antimicrobial stewardship, poor infection control practices and non-availability of essential antifungal agents.

In this study we have estimated 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 was reviewed and used when applicable (Table 1). Estimates were made in for the whole population, or specific populations at risk, as previously described in the LIFE methodology.

Results and discussion:

Based on our data analysis, in the 185 million people in Pakistan, an estimated 3.28 million people (1.78%) yearly are affected by a serious fungal infection (Table 2).

Cryptococcal meningitis and Pneumocystis pneumonia:

We estimated that yearly around 794 and 2,200 cases of cryptococcal meningitis and PCP occur in HIV infected patients respectively 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 a rate 2.5% and 9% of 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 center. 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 AIDS-defining illness. Variable rates of oesophageal candidiasis ranging from 14-33% 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.

Candidemia:

Based on data from India (14, 15), we estimated a high burden of candidemia in our population. Case fatality rate ranges from 23%-52% in reports from Karachi (38, 39) and 24% from a neonatal ICU (40). If a 40% mortality rate is used, then an estimated 15,498 people die with candidemia annually in Pakistan. Furthermore, candidemia 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 isolation of fluconazole resistant *Candida* species including *Candida auris* in the country (43).

Patients with upper gastro-intestinal disease and prolonged ICU stay have higher proportion of intraabdominal 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 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 gastrointestinal 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 0.14/1,000 population 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 ~9,815 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, proportion of population highest at risk for mucormycosis, i.e. diabetics, is higher in Pakistan than in India: 10% (50) versus 8% of general population, respectively (51).

Recurrent vulvovaginal candidiasis:

It is estimated that yearly 2,821,435 cases of recurrent vulvovaginal candidiasis occur in females of reproductive age group 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 that reports 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 ABPA and 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 94358 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 most common environmental fungus from Southern Pakistan in both indoor and outdoor environment (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% 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, CF prevalence of 1 in 9,000 population has been reported in South Asian Canadian immigrants as well as WHO estimates suggest a prevalence of 1 in 10,000-40,000 in 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 1,661 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 few cases not related to TB (i.e. due to sarcoidosis). CPA occurs in immunocompetent individuals with prior or existing pulmonary cavitory or non-cavitory disease (62, 63). Patients with prior pulmonary TB, sarcoidosis, ABPA, 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 diagnosis of CPA and ABPA are not available in many centers. 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 host with no apparent immune defect (64). Around 10,172 COPD patients develop invasive aspergillosis annually in Pakistan (using the 3.9% rate in hospitalized patients from China, based on culture and imaging) (17).

Assuming that 2% of all cancers as reported in Karachi, Pakistan are myeloid leukemia (19) and in these patients 10% will develop IPA (20) we estimated around 296 cases in this population. This is probably an underestimate as other patients with hematological malignancies are also at risk of IPA, therefore an equal number of cases was estimated for all other hematological 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 preexisting lung disease like COPD, critically ill patients in ICU, especially those given corticosteroids, diabetes and advanced liver disease (64). Invasive aspergillosis has been reported from Pakistan in patients with bone marrow, renal and liver transplant and hematological malignancy (65-67). A study conducted recently at our center on 69 patients revealed diabetes and chronic renal failure as 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 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 8-51% 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 etiology 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 burden of mycetoma is available from Pakistan. A study performed in Pakistan has reported that around 40% (5/12) of all cases of mycetoma in their center were due to fungi (70). Due to the paucity of exact data a burden of only 18-185 cases per year seems an underestimate.

Conclusion:

Fungal infections are common in Pakistan, but grossly under-diagnosed. 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 diagnosis of these conditions, better understand their local epidemiology, and institute preventative measures are called for.

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Table 1: Baseline population and prevalence of fungal infections

Disease	Baseline Population	Assumption	Prevalence	Ref
Cryptococcal meningitis	<p>HIV patients below CD4 cell count of 200 cells/uL</p> <p>Estimate: HIV patients in need of ART: 55,000</p> <p>All Cancer patients Estimate: 14,8041</p>	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	<p>2.5-9%</p> <p>0.0025%</p>	<p>7, 8, 9</p> <p>10, 11</p>
<i>Pneumocystis</i> pneumonia	<p>HIV patients below CD4 cell count of 200 cells/uL</p> <p>Estimate: HIV patients in need of ART: 55,000</p>	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, 8, 9
Oesophageal candidiasis	<p>HIV patients below CD4 cell count of 200 cells/uL</p> <p>Estimate: HIV patients in need of ART: 55,000</p>	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, 8, 9 12
Candidemia	<p>General population</p> <p>Estimate: 184,500,000</p>		21/100,000	13, 14, 15
Invasive aspergillosis	<p>Chronic obstructive pulmonary disease</p> <p>Estimate: Adults >40 y in Pakistan (20.4% of population) = 37,638,000</p> <p>Estimate: COPD prevalence (2.1% of adults >40y) =790,398 33% get hospitalised =260,831 admissions</p>	33% of COPD >40 years of age are admitted to hospital each year and 3.9% will develop IPA	3.9%	13, 16, 17

	Lung cancer patients Estimate: 6,800 Myeloid leukemia (2% of all cancers) Estimate: 2,961	2.6% 10% rate of IA in AML (over the year, not per neutropenic episode) + equal number for all other haematological conditions	2.6% 10%	10, 18 19, 20
Mucormycosis	General population Estimate: 184,500,000		14/100,000	13, 21
Recurrent vaginal candidiasis (4x/year +)	Adult female between age 15-50 years (50.6% of female population) Estimate: 47,023,921		6%	13, 22
Allergic Bronchopulmonary Aspergillosis	Adult asthmatic patients [61% of population are adults and of those 3.3% are asthmatic] Estimate: 3707897 Cystic Fibrosis Estimate: 18,450	2.5 of adult asthmatic patients in Pakistan will develop ABPA	2.5% 9%	13, 23, 24 13, 25, 26
Severe asthma with fungal sensitization	Adult patients with severe asthma (10% of adult asthmatic) Estimate: 370790	35% of adult asthmatic 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 cavitory disease Estimate: 70,999	35% (25-50%) of alive cases Pulmonary TB in 2014 will develop cavitory disease; of these 22% will develop CPA	22%	5, 27
	Pulmonary TB alive patients with non-cavitory disease Estimate: 131,855	65% (50%-75%) of alive cases Pulmonary TB in 2014 will develop non-cavitory disease; of these 2% will develop CPA	2%	27
	Sarcoidosis Estimate: 8,432	Incidence of sarcoidosis is 4.57/100000 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		0.01-0.1/100000	13, 34

Table 2: Estimated of burden of fungal infections

	Total burden	Number of infections per underlying disorder per year					Rate/100K
		None	HIV/AIDS	Respiratory	Cancer/Tx	ICU	
Cryptococcal meningitis	794	-	790* (344-1,237)	-	4	-	0.4
<i>Pneumocystis pneumonia</i>	2,200	-	2,200	-	-	-	1.2
Oesophageal candidiasis	3,231*	-	3,231 (1,925-4,537)	-	-	-	1.7
Candidemia	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 (4x/year)	2,821,435	2,821,435	-	-	-	-	1529 ^{&}
ABPA	94,358	-	-	92,697 + 1,661 [§]	-	-	51
SAFS	129,776	-	-	129776			70
Chronic pulmonary aspergillosis	72,438	-	-	71,932+506 [#]	-	-	39
Fungal keratitis	80,553*	80,553* (21,845-139,260)	-	-	-	-	44
Mycetoma	92*	92* (18-185)	-	-	-	-	0.05
Total burden estimated	3,280,549						1,778

*Mean incidence

§ In patients with cystic fibrosis

In patients with sarcoidosis

& rate for female population only