INFECTIOUS DISEASES JOURNAL

IDJ

of Pakistan

Published by the Medical Microbiology & Infectious Diseases Society of Pakistan

ISSN 1027-0299

Recognised and registered with the Pakistan Medical & Dental Council
NO.PF.11-F-96 (Infectious Diseases) 2560
College of Physicians & Surgeons, Pakistan
Indexed - *WHO EMRO*

January - March 2021 Volume 30 Issue 01

Designed & Published by:
Medishine Publications
A-452, Ground Floor, Block 7, K.A.E.C.H.S, Karachi.
Tel:34555263, E-mail:veterinaryguide@yahoo.com

Proprietor:
Medical Microbiology & Infectious Diseases Society of Pakistan
21 G /1, Block - 6, P.E.C.H.S., Shahrah-e-Faisal, Karachi. Ph: 0333-3977011
E-mail: info@mmidsp.com

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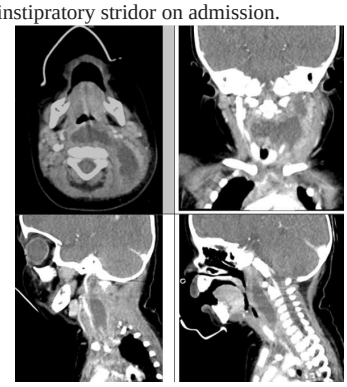
8 Month/F, with 5 day history of high grade fever, increasing respiratory distress and instipratory stridor on admission.



Description
CT Neck showing, Low-attenuation area containing multiple pockets of material with fluid density in the retropharyngeal location showing lateral extension intro the left parapharyngeal space, left cervical space and inferiorly extending upto the superior mediastinum and suprasternal region as detailed above. Overall findings are likely suggestive of an infective aetiology like retropharyngeal abscess. Underwent Exploratory incision and draininag with drain placement. Pus culture and Blood culture grew *MRSA*. Diagnosis: MRSA Retropharyngeal abscess

Courtesy : Ali Faisal Saleem, Associate professor, Paediatric Infectious Diseases, Aga Khan University, Karachi, Pakistan

Influenza to Follow COVID-19 Wave: the facts and flaws of influenza in Pakistan

Pneumonia is the leading cause of mortality for children less than 5 years old in Pakistan. Respiratory viruses such as *Influenza*, *Parainfluenza* and *Respiratory syncytial virus* (RSV) remain the most common etiology of infection amongst hospitalized patients with community acquired pneumonia.[1] CDC estimates for the pre-pandemic 2019-2020 influenza season disease burden was as high as 66.2 cases per 100,000 individuals with a test positivity rate of 16.8%. Global assessment of disease burden showed 19% test positivity rate from respiratory samples collected between November and December 2019.[2]

Since the year 2009 and the introduction of Influenza type A following the H1N1 pandemic, there has been a consistent rise in the number of annual cases of flu in Pakistan. Cases start appearing early in October with a peak incidence from December to February followed by a decline towards April. In the year 2016, the National Institute of Health Pakistan conducted testing of 300 samples from across the country out of which 110 were positive for influenza. Multiple studies post the H1N1 pandemic of 2009 showed a local test positivity rate of between 12-20%, with *influenza A* as the predominant strain in children.[3,4] As a result of lifestyle modifications during the COVID-19 pandemic such as social distancing, wearing of mask and effective handwashing, flu activity for the 2020-2021 season was the lowest since the CDC began reporting in 1997. This could potentially mean a decline in immunity for the upcoming flu season.

So which populations are at highest risk to be affected by seasonal influenza and would benefit most from the flu vaccine? According to the WHO, for countries who are currently expanding their influenza immunization program, pregnant females are at highest priority to receive the vaccine followed by children 6 months to 5 years of age, individuals with certain chronic medical conditions and older adults greater than 65 years of age. A systematic review and meta-analysis by Wang et al reported that in the year 2018, amongst children less than 5 years of age, there was an estimated 109 million new cases of influenza and 10.1 million influenza related acute lower respiratory infections (ALRI). In developing countries, there were 1.4 million cases of severe influenza-virus associated ALRI and 0.4 million cases of very severe influenza-virus associated ALRI.[5] The Global Initiative for asthma recommends influenza vaccination for individuals with moderate to severe asthma, while another systematic review by Vasileiou et al estimated the influenza vaccine to cause a 59-78% reduction in asthma related emergency department visits and hospitalizations.[6]

According to the most recent World Bank report of 2019, the mortality rate for children under 5 years of age is estimated to be 67 for every 1000 live births. A significant 70% of these deaths is secondary to infectious disease and its complications. To tackle this issue, the Extended Program on Immunization (EPI) was launched in Pakistan by WHO in the year 1978 and today includes immunization against tuberculosis, polio, tetanus, diphtheria, pertussis, H.influenza, hepatitis B, measles and rota virus. The importance of EPI cannot be stressed enough, being the primary source of immunizations for general population. Although EPI efforts have led to a significant reduction in childhood morbidity and mortality, the flu shot is yet to become a part of the program.

For the 2021-2022 season, there are currently two influenza vaccines available in the market, namely Influvac manufactured by Abbott and Vaxigrip manufactured by Sanofi. Both these vaccines are quadrivalent vaccines containing the following four strains: A/Victoria/2570/2019 (H1N1) pdm09-like strain, A/Cambodia/e0826360/2020 (H3N2)-like strain, B/Washington/02/2019-like strain, B/Phuket/3073/2013-like strain. This is the first year that the quadrivalent vaccine (IIV4) has been introduced in Pakistan, which compared to the earlier used trivalent vaccine (IIV3) has an additional Influenza B strain. An analysis by the US influenza Vaccine Effectiveness Network over four influenza seasons demonstrated IIV4 to provide additional protection against Influenza B as compared to IIV3.[7]

The cost of both these quadrivalent vaccines is around 12

Influenza Vaccine	Manufacturer	Type	Availability
Influvac	Abott	Quadrivalent	Available in Pakistan
Vaxigrip	Sanofi	Quadrivalent	Available in Pakistan
Afluria Quadrivalent	Seqirus	Quadrivalent	Not available in Pakistan
Flulaval Quadrivalent	GSK	Quadrivalent	Not available in Pakistan
Fluzone Quadrivalent	Sanofi	Quadrivalent	Not available in Pakistan
Fluarix Quadrivalent	GSK	Quadrivalent	Not available in Pakistan

dollars, which is a substantial sum of money for a country where the per capita income is less than 100 dollars per month. Alternatively, the cost of an in-patient hospitalization for severe pneumonia secondary to influenza exceeds 200 dollars, placing a significant economic burden on the health care system. This begs the question, will mass immunization of the high-risk population groups potentially reduce the economic burden flu places on our country each year? A large-scale study conducted within 25 EU countries estimated savings of 39 million euros from primary care visits with an additional savings of 1.52 billion euros from hospitalization if 100% of the high-risk population was vaccinated.[8]

In the current era with weakened immunity from either infection with COVID-19 or lack of exposure to other disease, we can certainly expect an extensive and severe flu season. With increasing costs of vaccination, there is dire need for a federal policy with the aim to increase influenza vaccine coverage in high-risk populations. This could be implemented in association with international programs as well as public-private partnerships such as the Global Alliance for Vaccines and Immunization (GAVI), which has previously supported the EPI program in Pakistan. The Ministry of Health, which has failed to recognize the needs of our population, should place their focus towards improving public health which would inadvertently reduce the economic burden of disease. It is certainly the need of the hour to develop a national "flu shot" program which would provide vaccination to high-risk population at the national, provincial and district level in collaborate with Civil Society Organizations (CSOs) to ensure adequate implementation of the program.

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1. *Shahzaib M Khan,*
MD, Instructor Pediatrics, Aga Khan University, Karachi, Pakistan

2. *Ali Faisal Saleem,*
MBBS, Associate Professor,
Pediatric Infectious Diseases,
Aga Khan University, Karachi, Pakistan
Email: ali.saleem@aku.edu

ORIGINAL ARTICLE

Factors Affecting Diagnostic Delay of Advance HIV Disease at Enrolment in the Indus Hospital, Karachi, Pakistan.

Jamil Muqtadir, Samreen Sarfaraz, Naseem Salahuddin

Department of Infectious Diseases, the Indus Hospital, Karachi, Pakistan.

Abstract

Background
Human immunodeficiency virus (HIV) infection is characterized by decreased CD4 cell count leading to opportunistic infections (OIs) and tumors. We have evaluated clinical profile, frequency and factors affecting the diagnostic delay of patients presenting with advanced HIV in Indus Hospital Karachi. There are limited studies in Pakistan which has evaluated risk factors for acquiring HIV infection therefore, this study was conducted.

Methods
A retrospective study was done at the Indus Hospital Karachi, from January to December 2017. All patients presenting with advanced HIV were included in the study. Clinical profile, frequency and factors affecting the diagnostic delay were evaluated.

Results
During study period 248, HIV patients were registered, of which 56(23%) had advanced HIV. Out of 56 patients, one was excluded due to Chronic Liver Disease. 45(82%) were male, 8(15%) were female and 2(4%) were transgender. Weight loss was the commonest symptom, followed by fever and loose stools. All patients had been visiting multiple health-care professionals before their final diagnosis was made. Among risk factors, exposure to female sex workers (34.9%) found to be commonest risk factor followed by injection drug use. Among the factors responsible for diagnostic delay, 94.5 % was missed diagnosis from health-care professionals, followed by lack of awareness from patients. Pallor was the commonest clinical examination finding, followed by oral thrush and lymphadenopathy. Hepatitis C was the most common coinfection, followed by syphilis and hepatitis B. Candidiasis was the most common opportunistic infection (27%), seven had oral candidiasis, seven had esophageal candidiasis and one had extensive gastrointestinal candidiasis. PCP (Pneumocystis carinii pneumonia) was the second most common opportunistic infection present in eleven 20%, followed by CMV (Cytomegalovirus) infection, MAC (Mycobacterium avium complex) colitis, cryptococcal meningitis and toxoplasmosis. Thirteen (23.2%) patients had other infections. 31 patients were followed, 12 were lost to follow-up, 8 died; 5 of PCP (Pneumocystis carinii pneumonia), 1 of cryptococcal meningitis, 2 of unknown cause while 4 were transferred to other facilities.

Conclusion
Advanced HIV represent about one third of all HIV patients. Weight loss was the commonest feature followed by fever and loose stools. Exposure to female sex workers was commonest risk factor for acquiring infection. Missed diagnosis was the commonest factor affecting the diagnostic delay.

Key words
Human immunodeficiency virus, opportunistic infections, Pneumocystis carinii pneumonia, Cytomegalovirus, Mycobacterium avium complex

Introduction

Human immunodeficiency virus (HIV) infection is characterized by decreased CD4 cell count and immunodeficiency, leading to opportunistic infections (OIs) and tumors.[1] According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 38 million people were infected with HIV globally in 2019.[2] According to UNAIDS, Pakistan is among the 11 countries in the Asia-Pacific which houses most of the people infected with HIV, and HIV prevalence in Pakistan by 2019 in adults and children is estimated to be 190000. According to a recent study, although there has been an increase in HIV prevalence in Pakistan, collective HIV infection rates in country are below 1% in general population (0.32%), increased prevalence is reported in IDUs (15.05%), sex workers (2.21%).[3] Persons living with HIV disease encounter intense and often unrelenting psychological and social stresses over the course of their illness. The stigmatizing nature of HIV and AIDS is a factor that affects delayed HIV testing by at-risk persons that leads to continuation behaviors, such as unprotected sex and needle sharing, and unknowingly transmitting HIV to others. Barriers to testing from the patient's perspective include delay in seeking medical care, fear of the financial burden brought by the disease, lack of education which diverts patients from taking medical care to hakims, faith healers and homeopaths, concerns about the impact of a positive result, fears around discrimination,

Corresponding Author: Jamil Muqtadir
HNo- A499/1, Ayesha Market near safora chorangi,
Gulistan-e-Johar, block-7,
Karachi, Pakistan.
Email: muqtdir169@yahoo.com

confidentiality, criminalization of risk behaviors, and limited knowledge about accessing testing or treatment on testing positive.[4] Reported concerns by clinicians include lack of knowledge about HIV and potential risk behaviors, lack of routine HIV screening even in the presence of associated symptoms, language barriers, and worry about informing individuals of a HIV-positive test result.[5]

To the best of our knowledge there is no study in Pakistan to see factors affecting the diagnostic delay of advanced HIV, therefore, we conducted study to evaluate the clinical profile, frequency and factors affecting the diagnostic delay of advanced HIV illness.

Material and Methods

This was a retrospective observational study conducted at The Indus Hospital Karachi, Pakistan, from January 2017 to December 2017. The Indus Hospital Karachi is tertiary care hospital that provides large number of in-patient and outpatient services in many specialties. The study included all patients with advanced HIV of either sex, aged 18-60years presenting in infectious diseases clinic, emergency room or inpatient and those with baseline CD4 <350/mm^3. Patients not meeting the criteria for advanced HIV, those stable on HIV and those having comorbid like Chronic Liver Disease and Chronic Kidney Disease were excluded from study. Data was collected using hospital management information system, data was collected on structured proforma. Detailed history and clinical examination of patients were done and labs were advised according to clinical suspicion of possible opportunistic infection for example lumber puncture for relevant investigations of cryptococcal meningitis/syphilis, brain imaging.

Statistical Analysis

Data entered and analyzed using SPSS version 24.0. Descriptive statistical analysis was performed. Mean (SD)/ Median (IQR) was computed as appropriate for all the quantitative variables like age, BMI, ESR, and CD4 count. Frequency along with percentage was computed for all the categorical variables like gender, physical examination, barriers in HIV diagnosis.

Definition

Advanced HIV Disease: Clinical stage IV or a CD4 cell count < 100 cells/µL at the time of HIV diagnosis.

Clinical Stage-IV: Patients diagnosed with Pneumocystis pneumonia, esophageal candidiasis and other features as explained by CDC.[6]

Delayed Diagnosis: A person diagnosed with HIV with a CD4 count below 350/mm^3 or an AIDS defining event, regardless of the CD4 count in the 6 months following HIV diagnosis.

Missed diagnosis: A person diagnosed with advanced HIV fulfilling the inclusion the criteria after visiting different health-care clinics for a period of >6months.

Results

248 patients were registered during that period, out of which 56 (22.6%) had advanced HIV. Out of 56, 1 patient was excluded due to Chronic Liver Disease Fig 1. 45(81.8%) were male, 8(14.5%) were female and 2(3.6%) were transgender. Demographic presentation and baseline biochemistry are shown in Tables 1 and 2. Weight loss was the commonest symptom, followed by fever and loose stools Fig 2. All patients had been visiting multiple health-care professionals before their final diagnosis was made. 12 patients denied history of any high-risk behavior. Among risk factors, exposure to female sex workers was found to be commonest risk factor followed by injection drug use. Four patients had history of blood transfusion, three had exposures to contaminated needles at health-care clinics and one had history of surgery Fig 3. Among the factors responsible for diagnostic delay, 94.5 % was missed diagnosis from health-care professionals, followed by lack of awareness from patients Fig 4. Eleven patients had anti tuberculosis therapy (ATT) in the past. Majority had taken ATT for presumed abdominal or pulmonary tuberculosis. Pallor was the commonest clinical examination finding, followed by oral thrush and lymphadenopathy. Three patients had positive Acid-fast bacilli (AFB) smear at the time of presentation, three had positive *Mycobacterium tuberculosis* (MTB) culture and four had positive Genexpert. Hepatitis C was the most common coinfection, followed by syphilis and hepatitis B. Candidiasis was the most common opportunistic infection (26.8%), seven had oral candidiasis, seven had esophageal candidiasis and one had extensive gastrointestinal candidiasis. PCP (Pneumocystis carinii pneumonia) was the second most common opportunistic infection present in eleven 19.6%, followed by CMV (Cytomegalovirus) infection, MAC (Mycobacterium avium

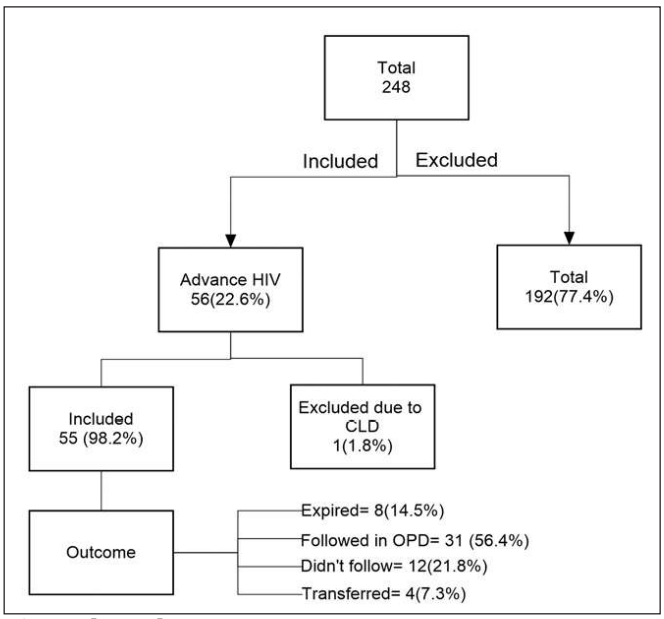

Fig 1. Flow Chart

HIV (human immunodeficiency virus), CLD (chronic liver disease), OPD (outpatient deparment)

Table 1: Demographic Information

Variables	n	%
Gender		
Female	8	14%
Male	45	82%
Transgender	2	4%
Place of Residence		
City	45	82%
Town	3	5%
Village	2	4%
Not recorded	5	9%
Religion		
Muslim	52	94%
Hindu	1	2%
Christian	2	4%
Marital status		
Married	33	60%
Un-married	19	34%
Divorced	2	4%
Not Recorded	1	2%
Number of children		
None	24	44%
1	5	9%
>1	18	33%
Not recorded	8	14%

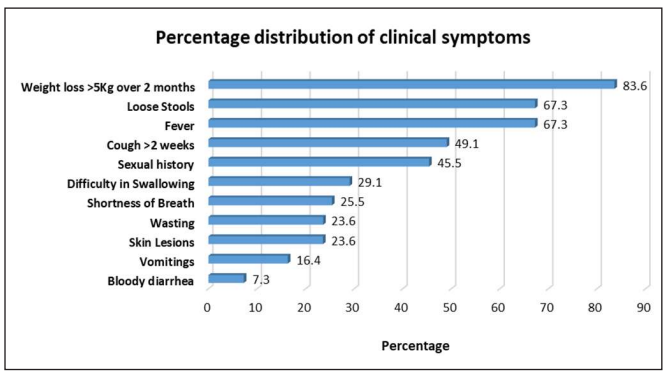

Fig 2. Frequency of symptoms

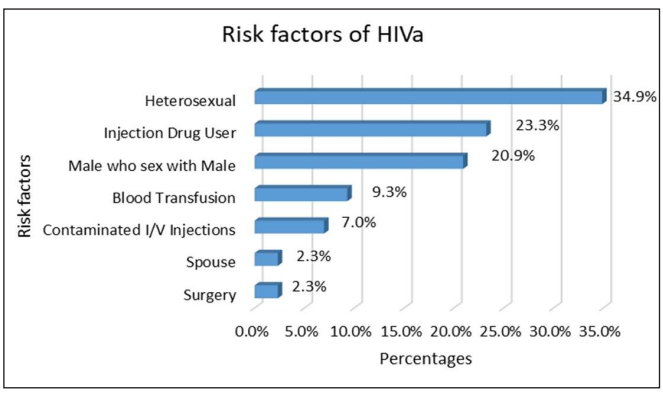

Fig 3. Risk factors for HIV

Table 2: Baseline Laboratory parameters

Age in Years	
Median (IQR)	31 (26 - 42)
Min-Max	18 – 67
BMI	
Median (IQR)	16.6 (14.4 - 18.8)
Min-Max	11 – 30
ESR	
Mean ± SD	67.52 ± 33.24
Min-Max	10 – 139
CD4 count	
Mean ± SD	91.6 ± 65.21
Min-Max	8 – 246
Hemoglobin	
Mean ± SD	10.48 ± 2.37
Min-Max	5.7 - 15.2
Total leucocyte count	
Median (IQR)	6220 (4622.5 - 8617.5)
Min-Max	1700 – 25040
Platelets	
Mean ± SD	268.74 ± 132.5
Min-Max	50 – 661
Creatinine	
Median (IQR)	0.7 (0.6 - 0.9)
Min-Max	0.4 - 1.5
Total Bilirubin	
Median (IQR)	0.4 (0.3 - 0.6)
Min-Max	0.2 - 1.1
Gama GT	
Median (IQR)	86 (43.5 - 195.5)
Min-Max	12 – 633
SGPT/ALT	
Median (IQR)	29 (18 - 51)
Min-Max	5 – 235
Alkaline phosphatase	
Median (IQR)	135 (89.5 - 300)
Min-Max	52 – 547
Lactate Dehydrogenase	
Mean ± SD	729.33 ± 423.95
Min-Max	301 – 1570

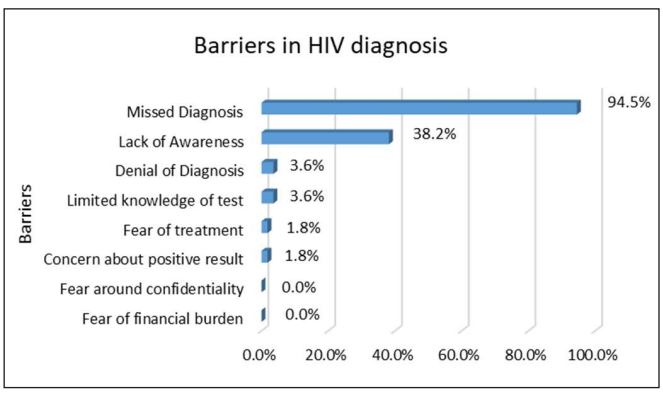

Fig 4. Diagnostic Barriers

complex) colitis, cryptococcal meningitis and toxoplasmosis.

Thirteen (23.2%) patients had other infections like lung abscess, infective endocarditis. 31 patients were followed, 12 were lost to follow-up, 8 died; 5 of PCP (Pneumocystis carinii pneumonia), 1 of cryptococcal meningitis, 2 of unknown cause while 4 were transferred to other facilities.

Discussion

The number of HIV/AIDS infections in Pakistan has been increasing at an alarming rate; from 2005 to 2015, the number of reported infections in Pakistan increased from 8, 360 to 45, 990 cases, the highest global average increase of 17.6% in history.[7] Joint United Nations Program on HIV/AIDS (UNAIDS) in 2017 reported that the prevalence of HIV in Pakistan between 15-49 years of age is 0.18% per 1000 population.

Delay in knowing the HIV positive status is challengeable in achieving the targets, results in the advancement of the disease that poses a less favorable clinical course, with reduced or incomplete treatment response, more rapid clinical progression, higher risk of mortality on the victims and burden to the healthcare system.

This study was conducted at large tertiary care hospital Karachi, Pakistan, is the first, to our knowledge, to quantify the delay in time from initial presentation to the health care system and ultimate diagnosis in patients with advanced HIV/AIDS. Xie J *et al*.[8] in Beijing, China also found that although a large proportion of patients had clues for immune compromise, yet they had not been offered HIV testing during previous medical visits. In Indonesia a cross sectional study Nugroho A *et al*,[9] consistent with our data that the length of diagnostic delay in among HIV positive was 6-12 months, Patient were hospitalized when severity of disease compelled them for an ADI (AIDS defining illness) and their CD4+T cell counts were below 250 cells/µL, as demonstrated by Lazar R *et al*[10] in New York 2103. On the other hand, limited knowledge of HIV, poverty, fear of positive results, denial of diagnosis was also responsible for delay in diagnosis. These barriers were also seen by Koirala S *et al*,[11] and Courtney LP *et al* in their study.[12]

Therefore, more research about clinician attitudes, behaviors and practices is essential. On the other hand, safe sex practices, awareness about HIV transmission are essential in order to identify feasible strategies to reduce barriers to testing in healthcare facilities.

About socio-demographics status Aniley *et al*[13] Choi BY *et al*[14] found that, mean age of patients with advanced HIV at the time of presentation was 26-41 years, prevalence was more common in females (64.1%) and majority of patients were living in urban areas (84%). Study done at 19 US cities by Wejnert C *et al*,[15] Out of total HIV-positive victim, 151 MSM (Male who have sex with males) (8%) and 184 PWID (People who inject drugs) (12%) were unaware of their infection. Similar risk factors with different ratio was found in the study done by and Uruena JMR *et al*.[16] HIV epidemic in Brazil remained with prevalence above 5% in specific populations, such as MSM, transgender women, female sex workers, heterosexual males and IDU reported by Benzaken AS *et al*.[17]

Persistent unexplained fever was most frequent presenting symptom among those advance HIV patients supported by Ansari JA *et al*.[18] In Gujrat, Pakistan HIV/AIDS out break and in Switzerland by Braun DL *et al*.[19] fever was the most common and genital ulcer were the least common clinical manifestation, whereas weight loss up to 5% and fever was second most common presenting illness in our patients. Loose stools, chronic cough, skin and oral lesion were other common findings.

Baseline demographic were same is our patients similar to study conducted by Boniphace I *et al*.[20] their CD4+T cell count was below 250 and total leukocyte count b/w 1700-25040 cu/ml compared to Sinha S *et al*.[21] In our study 21.8% of patients with advanced HIV had history of diagnosed /labeled / presumed as a case of TB, 78.2% had given no h/o TB in past. Other known previous co morbid was diabetes mellitus (3.6%), chronic liver disease (1.8%).

At the time of presentation, pallor, oral thrush, enlarged lymph nodes were the common clinical findings while dehydration, ascites, palpable spleen, palpable liver, reduced breath sounds and abnormal fundoscopic findings were also seen.

Most of our patients were co-infected with hepatitis C similar to study Heijnen M *et al*.[22] and most specific ADI diagnoses were *Pneumocystis jirovecii* pneumonia 11 (20%), consistent with study conducted by Lazar R *et al*.[10] Our findings were not consistent with study done by Qi T *et al*.[23] and McCarthy GA *et al*.[24] where Cryptococcus neoformans (22.7 %) and systemic Kaposi's sarcoma or lymphoma was most common ADI were found.

Syphilis 14(25.5%), Cytomegalovirus infection 5 (9%) and hepatitis B 3(5.5%) were also common in our study.

In our patients, normal radiograph was found in 53(96.4%) patients. AFB stain and culture positive came in 3 (5.5%), these findings show inverse relation with study done by Olatunji AA *et al*.[25]

From all included advance HIV positive 31(56.4%) patients properly followed in OPD, 12 (21.8%) loosed follow up and 8 (14.5%) were expired.

Study Strengths and Limitations

Strength of our study was that despite many studies on HIV related problems, there was no study conducted on factors responsible for diagnostic delay in Pakistan before. Therefore,

this study would probably be the first on this specific issue. The main limitations of the present study include the cross-sectional design where cause cannot be attributed, a single-center experience, low female representation in the study cohort and nonrandomized study design. Hence, the figure does not reflect true frequency and severity of the disease. Secondly, there were some confounding factors in this study, such as age, race, diet, travel to endemic area, treatment of HIV and so on. All the study participants were also selected without specification that could increase the recall bias. Moreover, this study was conducted with small sample size and in urban environment, representing advanced cases of HIV therefore, cannot be applied to patients with asymptomatic or mild HIV infection therefore; the results might not be generalizable to larger populations.

Conclusion

Advanced HIV represent about one third of all HIV patients. Weight loss was the commonest feature followed by fever and loose stools. Exposure to female sex workers was commonest risk factor for acquiring infection. Missed diagnosis was the commonest factor affecting the diagnostic delay.

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ORIGINAL ARTICLE

Coronavirus Related Fears among Residents of Karachi, Pakistan

Afreen Faiza*, Aymen Munazza**

* Ilma University Formerly IBT, Karachi, Pakistan,
** Aisha Steel Mills Limited, Karachi, Pakistan

Abstract

Objective
The emerging epidemic coronavirus (COVID-19) crisis rattled nearly every sphere of life across all over the globe, aim of the study was to explore fears produced due to the swift spread of the deadly virus among residents of Karachi city, Pakistan.

Method
A 10–item Coronavirus Fear Questionnaire (CVFQ) with good reliability (α=.75, p<.01) purposely constructed based on informal interviews from the general population and administered on (N=264) participants invited via an online Google based survey.

Results
Outcomes showed the prevalence of fears related to the infection to oneself (76.5%), family (84.5%), contagious transmissions (62.9%), death of loved ones (72.3%), financial constraints (80.7%), increase in prices (85.2%), disease rumors (80.7%), restriction of mobility (71.2%), and social rejections (61.7%).

Conclusion
It was concluded that residents of Karachi possess different fears related to COVID-19, which warrants appropriate psycho-social attention.

Keywords
Coronavirus, Questionnaire, Reliability, Fears, Karachi, Pakistan

Introduction

Coronavirus (COVID-19) is the third viral catastrophe after SARS-CoV[1] and MERS 2012 [2], which erupted in late 2019 in which an increasing number of individuals complained about pneumonia-like symptoms. The origin of the virus was mysterious and assumed to emerge from the seafood market located in Wuhan, China[3] spreading from Wuhan to other cities in China, Asia, engulfing the entire world.[4]

In Pakistan, the first case of coronavirus was reported on February, 2020 with 1,856 cases and 25 deaths till March, 2020[5] which increased up to 37218 cases, 10,155 recoveries with 803 Deaths till May, 2020[6]. To curb the spread of the virus, the Government of Pakistan announced public health safety measures which include travel restrictions, social distancing, quarantine policies and closure of educational organizations.[7]

Pakistan is the fifth densely populated region with poor economic conditions[8], Lower and Middle-Income Countries (LMICs) juggle with lack of workforce distribution in health areas, poor infrastructure, and lower mental health awareness[9]; lack of adequate supplies of beds, ventilators, oxygen cylinders, personal protective equipment and hand sanitizers.[10] In such a scenario, covid-19 posed a serious threat in Pakistan as it is already battling with numerous transmittable and non-transmittable infectious diseases. [11]

In LMICs there is a narrow understanding of covid-19 related perceptions.[12] Likewise, in Pakistan, political and religious groups pose resistance against governmental orders.[13] In Pakistan, the tradition of a joint family system is prevalent, people live in closed spaces hence, quarantine measures and social distancing challenged the physical as well as psychological health of individuals.[8]

Covid-19 not only threatened the physical health of individuals but also adversely affect the mental, social and psychological well-being of people.[14] Nearly half of the participants showed medium to high levels of psychological effects following an early outbreak of COVID-19.[15] Studies carried out considering population from high and LMICs revealed that covid-19 related fears are closely linked with psychological disorders.[16,17,18]

In case of epidemic outbreaks, and during epidemic conditions, uncertainty produces fears and anxieties among healthy people.[19] Lack of management of negative emotions aroused due to pandemic outbreaks creates prolonged psychological disorders,[20,21] which possibly linger even after crises subsides. It is believed that unconventional and novel dangers induce greater levels of anxiety as compared to familiar ones.[22,23] Worldwide epidemic prevalence of COVID-19 warrants clinical attention towards the mental health of individuals.[24]

However, the majority of psychological research related to covid-19 contributed by China, the United States and European regions.[25] Developing countries possess an augmented level of

Correspondence Author: Afreen Faiza,
Ph.D Psychology
Research Associate, Ilma University Formerly IBT,
Karachi, Pakistan
E-mail: afreenfaiza2014@gmail.com

fear about epidemic than epidemic itself [26,27,28] creates pressing need to carry out covid-19 related investigations in LMICs to effectively comprehend situation.[25] It is necessary to cater to the psychological issues of individuals to effectively manage and control any pandemic situations.[29,30,31] Therefore, it is crucial to explore the psychological effects of covid-19 among the Pakistani population for detection and psychological intervention.

The purpose of the study was to explore the prevalence of general fears related to covid-19 among residents of Karachi, Pakistan.

- Ø To investigate covid-19 related infection fears among residents of Karachi city.
- Ø To investigate Covid-19 related fears about financial and social issues among residents of Karachi city.

Materials and Method

The study was carried out during the initial covid-19 outbreak and strict lockdown periods in Karachi city (March/ April 2020). Due to social distancing policies, all respondents were approached online via different social networking sites (Facebook, WhatsApp, Instagram, LinkedIn).

It was an exploratory study for which CVFQ was purposively designed in successive stages. Individuals (n=30) with an age ranged from 19 to 40 years selected for an informal interview. open-ended questions such as What are the main reasons for corona related anxiety/fear among the public? What are the thoughts and emotions come to your mind when someone speaks to you about the coronavirus? were asked from key informants via online interviews (Zoom, Microsoft Teams, WhatsApp calls) to explore common reasons for fears related to the COVID-19.

The verbatim was qualitatively analyzed for key ideas and themes. Fifteen items were written based on two conceptual categories: fear of viral infection; personal and social insecurities. Dichotomous categories (yes/no) were decided to score responses. To ascertain content validation, fifteen items were given to two subject experts for the determination of face validity, specificity, and content adequacy. Items were modified according to expert suggestions. Twelve items were deleted due to a lack of clarity.

Pilot Study was done on a sample of (n=20) individuals with a requested to identify clarity and aptness for further refinements. Two items were discarded due to ambiguity. The final pool of 10-item-CVFQ was finally administered for determination of internal consistency on a sample of 264 (111 male & 153 female) individuals, age ranged from 19-47 years recruited over one month (March to April 2020). All individuals were Karachi residents and currently present in the city during the lockdown period. The ethical criteria of research were carefully considered. All respondents have fully described the purpose, right to refuse participation or leave in the middle of the study. They were also ensured about confidentiality that data will only be used for research publications without identification of personal information and only consented participants were included in the study. Statistical Package for Social Sciences (SPSS) version 22 used for data analysis.

Results

Demographic Profile (represented in Table 1) shows that out of 264 Participants, 153 (58%) females and 111(58%) males. The age of 88 individuals were ranged from 19-25 years (33.3%); 92 individuals aged between 26-32 years (34.8%); 44 participants aged between 33-39 years (16.7%), 24 respondents age ranged from 40-46 years (9.1%) and 16 participants age ranged from 47 and above (6%). 81 individuals completed the bachelor's degree (30.6%), 119 participants attained maters (45.1%), 64 respondents attained a doctoral degree (24.2%).

163 participants were single/ never married (61.7%), 93 were married (35.2%) and 8 respondents were divorced/ separated (3%).

Responses of participants for CVFQ (Table 3) shows 202 participants reported fear of covid-19 infection (76.5%), 223(84.5%) showed fear of infection to family members, 166 (63%)showed fears that infection is inescapable, 191(72.3%)showed fear of death, 199(75.4%) feared about the delay of vaccine, 225(85.2%)feared about increases in prices,

Table 1: Shows the frequency and percentage counts of individuals who participated in the study (N=264).

Demographics		Frequency	Percentage (%)
Gender	Male	111	42
	Female	153	58
Age	19-25 years	88	33.3
	26-32 years	92	34.8
	33-39 years	44	16.7
	40-46 years	24	9.1
	47 years	16	6.0
Education	Bachelors	81	30.6
	Masters	119	45.1
	Doctorate and above	64	24.2
Marital Status			
	Single/ never married	163	61.7
	Married	93	35.2
	Separated/ Divorced	8	3.0

Table 2: Internal consistency for 10-items Coronavirus Fear Questionnaire (CVFQ) (N=264)

Do you feel anxiety /worry about?	*r- values*
Infection from COVID-19?	.406
Children/ elderly parents/ grandparents will be infected from COVID-19?	.500
Infection of COVID-19 is inescapable?	.388
Death of loved ones (family, friends, relatives) due to COVID-19?	.373
The vaccine will take a longer time to control COVID-19?	.359
Increase in prices (food/grocery/sanitizes/ soaps) due to COVID-19?	.356
Financial problems (unemployment/job loss /business loss) due to COVID-19?	.394
Rumors spread in media (news channels, internet, social networking sites)?	.360
Limitation of activities (travelling, social gatherings) due to COVID-19?	.349
Social rejections by other people due to COVID-19 contamination?	.456
Overall CVFQ	.750

CVFQ=Coronavirus Fear Questionnaire, *p<.01

Internal consistency of CVFQ in Table 2 shows that the values for the 10-item questionnaire lie in acceptable range of (α=.35-.5, p<.01). Good indices of overall reliability for CVFQ was found (α=.75, p<.01).

Table 3: Shows the percentage and frequency counts (f) for responses of participants on CVFQ (N=264)

Do you feel anxiety /worry about?	No f (%)	Yes f (%)
Infection from COVID-19?	62(23.5)	202(76.5)
Children/ elderly parents/ grandparents will be infected from COVID-19?	41(15.5)	223(84.5)
Infection of COVID-19 is inescapable?	98(37.1)	166(62.9)
Death of loved ones (family, friends, relatives) due to COVID-19?	73(27.7)	191(72.3)
The vaccine will take a longer time to control COVID-19?	65(24.6)	199(75.4)
Increase in prices (food/grocery/sanitizes/ soaps) due to COVID-19?	39(14.8)	225(85.2)
Financial problems (unemployment/job loss /business loss) due to COVID-19?	51(19.3)	213(80.7)
Rumors spread in media (news channels, internet, social networking sites)?	51(19.3)	213(80.7)
Limitation of activities (travelling, social gatherings) due to COVID-19?	76(28.8)	188(71.2)
Social rejections by other people due to COVID-19 contamination?	101(38.3)	163(61.7)

213(80.7%) showed fears about financial problems and rumors spread by media, 188(71.2%) showed fears about limitation of activities and 163(61.7%) respondents showed fears about social rejections. Results imply that most participants reported covid-19 related fears.

Discussion

The purpose of the study was to explore the prevalence of general fears related to covid-19 among residents of Karachi, Pakistan. It investigates different fears related to covid-19 (infection fears, fears about financial and social issues) among Karachi residents. For this purpose, a short survey questionnaire (10-item, CVAQ-10 item) was designed which demonstrated acceptable reliability coefficients.[32] The outcomes of the study showed an overall greater prevalence of Covid-19 related fears among residents of Karachi city. Results are congruent with earlier investigations which revealed a larger proportion of residents in different regions of the world (USA, China) reported covid-19 related anxieties.[33,34]

Findings of the present study showed that the majority of Karachi residents disclosed covid-19 related infection fears such as fears about the infection to oneself (76.5%), family (84.5%), contagious transmissions (62.9%) and death of loved

ones (72.3%). Present findings are in agreement with an earlier study which showed (94%) Karachi residents reported fear about the health of family members due to covid-19.[35] In the USA, more than half of the population showed anxiety related to covid-19 transmissions[36] and in China, 30% population declared fear of death of one's self due to covid-19 infections.[37] Greater prevalence of fears possibly denotes fact that epidemic conditions accelerate uncertainties and fears about being infected and transmission of disease to others and death likely to impact negatively on psychological states [38] and increase fears related to spreading of infection in family members.[39]

Covid-19 related fears about financial and social issues among residents of Karachi city showed people endorsed presence of fears about the hike in prices (85.2%), financial constraints (80.7%) rumor spread (80.7%), restriction of mobility (71.2%), and social rejections (61.7%). Greater fears related to financial matters during a pandemic is possibly due to changes in work patterns and social distancing which creates a sense of isolation and helplessness, people feel sense of insecurities because of the decline in economic conditions.[40] Also, closures of business following epidemic outbreaks create job losses and financial issues likely to diminish the psychological conditions of people.[41] Research showed that the spread of false covid-19 related information via media creates higher levels of fear (84%) among Karachi residents.[35] This was also indicated by the study which showed that lack of knowledge and false news related to creates fear and anxiety among the Chinese population.[42,43] A possible reason for higher Covid-19 fears related to disease rumors (80.7%) includes erroneous information and rumors about the disease which creates misunderstandings and increased fears among the public.[44]

Higher levels of Covid-19 related fears about the restriction of mobility (71.2%), and social rejections (61.7%) affirmed by earlier studies which showed during pandemics, stringent quarantine and other health safety measures cause discrimination, societal rejections financial hardships and stigmatization.[45,46]

Possible explanations denote the notion that during epidemics, the inability to participate in daily routine activities creates distress[47] and social rejections followed by epidemic outbreaks create fears among individuals.[48,49]

Conclusion

The present study showed an alarming prevalence of COVID-19 related fears among residents of Karachi, Pakistan. The generalization of present outcomes should be made with cautions because of the small sample size and limited focus on participants from Karachi city. It is recommended to carry out future investigations considering the population of different cities of Pakistan. Also, the study could be replicated to investigate covid-19 related fears among the population diagnosed with psychological and physical/ chronic diseases.

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ORIGINAL ARTICLE

Spectrum of Invasive Yeast Infections in Neonates, Children and Adults in Pakistan Over Five Years: 2015-2019

Salima Rattani*, Saba Memon**, Kauser Jabeen*, Joveria Farooqi*

*Department of Pathology and Laboratory medicine, Aga Khan University Hospital, Karachi, Pakistan
**Department of Microbiology, Karachi University, Karachi, Pakistan

Abstract

Background
There is a widening population of hosts susceptible to invasive yeast infections secondary to prolonged hospitalization, immunocompromised, use of medical devices, broad-spectrum antibiotics, and survival of extremely vulnerable populations. Here we describe the changing spectrum of invasive yeast infections in neonates, children, and adults in the last 5 years in Pakistan.

Methods
Records of archived yeast isolates from Jan 2015-May 2019 kept at the Aga Khan University Clinical Laboratories, section of Microbiology in Karachi, were retrieved for analysis. Frequencies of different *Candida* and non-*Candida* species isolated over the last five years were computed and compared for age groups using chi-square test.

Results
A total of 1119 non-duplicate isolates were identified, of which 992 were invasive specimens. *Candida* species made up 86.7%, 88.2% and 88.1% of all invasive yeasts in neonates, children, and adults, respectively. Rare *Candida* were most common group in neonates, *C. tropicalis* predominated in children and *C. auris* topped the list of invasive yeasts in adults. The distribution of invasive yeasts between neonatal, pediatric and adult age groups was different significantly ($p<0.001$). Change in spectrum of invasive yeast over the years was significant for neonates ($p=0.017$), and adults ($p=0.003$). Fluconazole resistance in yeast isolated from neonates, children and adults was found to be 8%, 23% and 36% respectively.

Conclusion
It is essential to monitor the spectrum and antifungal resistance trends of yeast infections in neonates and children as they are the population where there is greatest diversity of invasive species, not limited to Candida species.

Corresponding Author: Joveria Farooqi,
Department of Pathology and Laboratory Medicine,
Aga Khan University,
Stadium Road, Karachi, Pakistan
Email: joveria.farooqi@aku.edu

Keywords
Invasive yeast infections, spectrum, Candida, antifungal resistance, neonates, children, adults.

Introduction
The incidence of invasive yeast infections is on the rise due to expanding population of susceptible hosts. These infections can occur secondary to prolonged hospitalization, use of medical devices, drugs or diseases affecting immune response, broad-spectrum antibiotics, and survival of extremely vulnerable populations like preterm babies, patients with solid organ or hematological malignancies and geriatrics.[1-3]

The spectrum of invasive fungal infections includes fungemia, intra-abdominal infections, septic arthritis, iatrogenic and neonatal meningitis. *Candida* species are most commonly involved, however *Cryptococcus* species, *Trichosporon* species, *Malassezia* species and others are also implicated.[3]

In a previous study from our center on spectrum of candidiasis (2006-2009), neonatal and pediatric age group differed greatly from the adults.[1] To explore this difference in neonatal and pediatric group further, we conducted a review of our laboratory data from the last 5 years.

Methods
This study reviewed laboratory data of the Aga Khan University Hospital (AKUH) laboratory, Karachi, Pakistan. Records of reported yeast isolates from Jan 2015-May 2019 were retrieved for analysis.

Invasive yeast was defined as isolates yielded from blood, CSF, wounds, intraabdominal collections, central venous lines, and other sterile fluids positive for yeast (*Candida* species, *Ustilago* species, *Trichosporon* species, *Rhodotorula* species and *Cryptococcus* species). Duplicate cases were excluded if more than one culture from a single patient was positive for the same organism. The data was divided into 3 groups based on patient age including neonates (0 to 30 days of life), pediatric patients (>1 month to <18 years) and adults (≥18 years).

Conventional phenotypic methods were used to identify yeasts isolated from different cultures. These included productions of

a germ tube, morphology on BBL BiGGY Agar (BD) and chrome agar, growth with cycloheximide, urease production, and morphology on cornmeal/Tween 80 agar. API 20C AUX® (bioMe´rieux) was used to generate an identification profile for isolates which could not be identified by these methods, that is, species other than *Candida albicans, C. tropicalis, C. parapsilosis* and *C. glabrata*. Those candida species other than *C. albicans, C. tropicalis, C. parapsilosis, C. glabrata, C. krusei* and *C. auris* were termed "rare *Candida* species". For *Ustilago* species, identification was done using phenotypic methods including microscopic morphology (string bean pseudohyphae), growth on different media (initially mucoid, later dry membranous colonies) and susceptibility pattern (resistance to echinocandins and flucytosine).

Antifungal susceptibility testing for fluconazole and voriconazole was performed by disc diffusion for *C. albicans, C. tropicalis, C. parapsilosis* and interpreted according to CLSI M60. For all other non-*C. albicans* candida species antifungal susceptibility testing was performed by broth microdilution with fluconazole, itraconazole, voriconazole, posaconazole, anidulafungin, caspofungin, micafungin and amphotericin B as described by the Clinical and Laboratory Standards Institute (CLSI) using Sensititre™ YeastOne™ YO9 AST Plate. *Candida glabrata, Candida krusei* MIC were reported according to CLSI guidelines.[4] For other candida species, fluconazole was considered resistant at an MIC of ≥4 µg/ml in accordance with clinical breakpoints for fungi by EUCAST.[5] In the absence of clinical breakpoints, epidemiological cut-off values (ECVs) were used to interpret MICs as those conforming to wild-type or non-wild-type for a particular antifungal agent against a specific species based on CLSI guidelines.[5,6]

Data was exported from laboratory information system to Microsoft Excel 2010 from the relevant study period and duplicates were removed as described. Data was then imported into Stata/SE version 12.1 (2012) for analysis. Frequencies of different *Candida* and non-*Candida* species isolated over the last 5 years were computed and compared for age groups using chi-square test. Hypothesis of a change in the spectrum over the years among each age group was also tested.

Results

A total of 1119 non-duplicate isolates were identified, of which 992 were invasive specimens: from blood (n=833), CSF (n=51), wounds (n=47), intra-abdominal collections (n=36), central venous lines (17) and other sterile fluids (8). The patients were divided into neonates (n=259), pediatric age group (n=253) and adults (n=477). *Candida* species made up 86.7%, 88.2% and 88.1% of all invasive yeasts in neonates, children, and adults, respectively. The most common group in neonates was a diverse group of rare *Candida* species (including *C. lusitaniae, C. guilliermondii* and *C. pelliculosa, C. utilis, C. kefyr, C. famata, C. rugosa, Kodamaea ohmeri* and unidentified *Candida* species); *Ustilago* species were the most common non-candida yeast (Table 1). In children, the most common species was *C.*

Table 1: Spectrum of invasive yeasts in neonates 0 to 30 days of life

Organism	2015	2016	2017	2018	2019	2015-May 2019	%
Candida albicans	11	2	8	4	3	28	10.0%
Candida krusei	3	0	2	0	2	7	2.5%
Candida glabrata	0	0	0	1	0	1	0.4%
Candida parapsilosis	9	7	17	4	3	40	14.2%
Candida tropicalis	9	16	29	22	1	77	27.4%
Rare *Candida* species	24	21	37	23	20	125	*44.5%
Candida auris	0	2	1	0	0	3	1.1%
All Candida	56	48	94	54	29	281	86.7%
Ustilago species	2	6	10	10	5	33	±10.2%
Trichosporon species	2	1	1	0	0	4	1.2%
Rhodotorula species	2	0	3	1	0	6	1.9%
Malassezia species	0	0	0	0	0	0	0.0%
Cryptococcus neoformans	0	0	0	0	0	0	0.0%
Cryptococcus non-neoformans	0	0	0	0	0	0	0.0%
Kloeckera species	0	0	0	0	0	0	0.0%
All Non-Candida	6	7	14	11	5	43	13.3%
All Yeasts	62	55	108	65	34	324	

p-value: 0.017

*most common *Candida* species causing invasive yeast infections

±most common non-*Candida* species causing invasive yeast infections

Rare *Candida* species: *Candida* species other than *C. albicans, C. tropicalis, C. parapsilosis, C. glabrata, C. krusei* and *C. auris*

tropicalis; *Ustilago* was again the most common non-candida yeast (Table 2). Most notably in adults, *C. auris* topped the list of invasive yeasts, while *C. neoformans* was the most common non-candida yeast (Table 3). There was a significant difference in the distribution of invasive yeasts between neonatal, pediatric and adult age groups ($p<0.001$). Change in spectrum of invasive yeast over the years was significant for neonates ($p=0.017$), and adults ($p=0.003$); however, we could not demonstrate a significant difference in spectrum within infants and children ($p=0.417$). Fluconazole resistance in yeast isolated from neonates was found to be 7.9% while it was 22.5% in infants and children, and 36.3% in adults.

Discussion

Candida species were the most common of all invasive yeasts in neonates, children, and adults. The spectrum of invasive yeast infections has changed significantly over the years with rare *Candida* species (including *C. lusitaniae, C. guilliermondii* and *C. pelliculosa* to name a few) being the most common cause in neonates and *C. auris* being the most common invasive yeast infection in adults. However, there was no significant change in spectrum of these infections among infants and children.

The spectrum of invasive yeast infections is changing. Studies show candidemia to be the most common cause of invasive yeast infection worldwide[7,8] similar to our study.

Candida albicans had been the predominantly reported *Candida* species associated with neonatal candidemia in Pakistan before 2006[2]. Later studies indicated that *C. tropicalis* became the most common candida species identified in neonates with candidemia[1,9]. In contrast, study from India shows *C. parapsilosis* and *C. glabrata* to be the most common *Candida* species as a cause of neonatal candidemia during recent years.[10] Our study shows rare *Candida* species (including *C. lusitaniae, C. guilliermondii* and *C. pelliculosa* to name a few) to be the most common cause of invasive yeast infections followed by *C. tropicalis* (27.4%) and *C. parapsilosis* (14.2%). *C. glabrata* (0.4%) was rarely seen in our neonatal population.

Studies from developed countries show *C. parapsilosis* followed by *C. tropicalis* to be the most common yeast causing infections in children specifically in patients with hematologic malignancies, *C. albicans* in patients needing intensive care followed by *C. parapsilosis* and *C. albicans* in children with solid organ transplants.[11,12] Older studies from developing countries (before 2015) show *C. albicans* to be most common amongst children[1,13] in contrast to our study where *C. tropicalis* was found to be the most common cause of invasive yeast infection in children in our population.

Some studies show *C. albicans* to be the most common cause of invasive yeast infection in adults.[14,15] Studies from Pakistan report non-*C. albicans candida* species like *Candida tropicalis*

Table 2: Spectrum of invasive yeasts in Children >1 month to <18y

Organism	2015	2016	2017	2018	2019	2015-May 2019	%
Candida albicans	8	2	10	3	6	29	16.9%
Candida krusei	0	0	1	1	1	3	1.7%
Candida glabrata	3	0	1	0	2	6	3.5%
Candida parapsilosis	4	1	13	5	2	25	14.5%
Candida tropicalis	7	10	14	9	9	49	*28.5%
Rare *Candida* species	7	3	6	8	5	29	16.9%
Candida auris	2	5	7	11	6	31	18.0%
All Candida	31	21	52	37	31	172	88.2%
Ustilago species	5	1	3	3	6	18	±9.2%
Trichosporon species	0	0	1	0	1	2	1.0%
Rhodotorula species	0	0	1	0	0	1	0.5%
Malassezia species	0	0	0	0	0	0	0.0%
Cryptococcus neoformans	0	0	0	0	1	1	0.5%
Cryptococcus non-neoformans	0	0	1	0	0	1	0.5%
Kloeckera species	0	0	0	0	0	0	0.0%
All Non-Candida	5	1	6	3	8	23	11.8%
All Yeasts	36	22	58	40	39	195	

p-value: 0.417

*most common *Candida* species causing invasive yeast infections

±most common non-*Candida* species causing invasive yeast infections

Rare *Candida* species: *Candida* species other than *C. albicans, C. tropicalis, C. parapsilosis, C. glabrata, C. krusei* and *C. auris*

Table 3: Spectrum of invasive yeasts in Adults

Organism	2015	2016	2017	2018	2019	2015-May 2019	%
Candida albicans	17	9	28	17	13	84	20.0%
Candida krusei	0	0	3	3	0	6	1.4%
Candida glabrata	7	5	21	15	25	73	17.4%
Candida parapsilosis	16	7	32	11	10	76	18.1%
Candida tropicalis	17	12	15	9	9	62	14.8%
Rare *Candida* species	4	4	8	4	6	26	6.2%
Candida auris	6	7	40	26	14	93	*22.1%
All Candida	67	44	147	85	77	420	88.1%
Ustilago species	0	0	2	1	0	3	0.6%
Trichosporon species	3	0	1	4	1	9	1.9%
Rhodotorula species	3	0	0	0	2	5	1.0%
Malassezia species	0	0	0	0	0	0	0.0%
Cryptococcus neoformans	7	2	12	10	7	38	±8.0%
Cryptococcus non-neoformans	0	0	0	1	0	1	0.2%
Kloeckera species	1	0	0	0	0	1	0.2%
All Non-Candida	14	2	15	16	10	57	11.9%
All Yeasts	81	46	162	101	87	477	

p-value: 0.003
*most common *Candida* species causing invasive yeast infections
±most common non-*Candida* species causing invasive yeast infections
Rare *Candida* species: *Candida* species other than *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei* and *C. auris*

and *C. parapsilosis* were the most common cause of invasive yeast infections in adults.[1,16,17] In contrast our study found an increase in isolation of *Candida auris* in adults as a cause of invasive yeast infections.

Ustilago species were the most common non-candida species causing invasive yeast infections in neonates and children. These are yeast-like fungi which are plant pathogens and have rarely been incriminated in human infections.[19] According to a few case reports, it causes invasive fungal infections globally and is resistant to flucytosine, fluconazole and echinocandins, this pathogen assumes a greater clinical significance.[19] However further patient details are needed before determining its clinical significance.

Cryptococcus neoformans, at 8%, was found to be the most common non-candida species causing invasive yeast infections in adults like other studies.[20-22] Globally, most cases of cryptococcosis are seen in HIV patients. A previous study from our center identified a large group of non-HIV risk factors for cryptococcosis, e.g., transplant, use of immunosuppressive agents, chronic infections like hepatitis B and C, autoimmune diseases, and malignancies.

There was a very high incidence of fluconazole resistance in yeasts isolated in adults followed by children. This could possibly be due to an emergence of *C. auris* infections in adults (22.3%) and children (18%) versus neonates (1.1%).

The limitations of our study include the retrospective nature of study due to which clinical significance of uncommon organisms, and risk factors could not be assessed for acquiring invasive yeast infections. Another limitation of our study was that all the yeasts were identified by phenotypic methods which might have led to improper identification of rare and unknown *Candida* species.

The strength of this study is that it shows the etiologic spectrum and antifungal resistance of invasive yeasts infection amongst neonates, children, and adults. It is necessary to learn a center's local epidemiology due to differences in the distribution of these species among different pediatric intensive care units and hospitals.

It is essential to monitor the spectrum of yeast infections in neonates and children as they are the population where there is greatest diversity of invasive species, not limited to Candida species. Emerging pathogens are most likely to arise from this population, including resistant strains, hence, it is also important to monitor resistance trends.

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A Case of Poly Drug Resistant –Tuberculous sternal osteomyelitis in an immunocompetent male.

Beenish Syed*, Fivzia Herekar**

*Department of Internal Medicine, Liaquat National Hospital, Karachi.
** The Indus Hospital, Karachi. Postal Address: The Indus Hospital, Plot C-76, Sector 3 1/5, Opposite Korangi Crossing Road, Karachi

Abstract
Primary Sternal Tuberculosis is rare and accounts for < 1% cases of skeletal TB. Most cases are reported from TB endemic countries. Drug resistant sternal tuberculosis has been sporadically reported in literature. We present here a case of polydrug resistant Tuberculosis of sternum in an immunocompetent male. AFB culture showed resistance to Streptomycin(S) and Isoniazid (H). Patient was started on modified ATT with HREZ + Levofloxacin + Amikacin. Total duration of treatment was 10 months. Poly drug resistant TB can lead to amplification of resistance and MDR - TB on treatment with the standardized 1st line drugs. DST results at baseline and previous treatment history should be considered to design the appropriate regimen. At least 3 or 4, likely effective drugs should be selected for duration of 9-18 months.

Keywords
Amplification of resistance, Drug sensitivity testing, Treatment failure

Background
Tuberculosis still accounts for the most prevalent of all infectious diseases with more than 10 million people getting affected annually and approximately 1.7 million deaths.[1] Osteoarticular involvement is seen in up to 10% of cases of extra pulmonary TB.[2] Primary Sternal Tuberculosis is even rarer and accounts for < 1% cases of skeletal TB. Most cases are reported from TB endemic countries like India, Pakistan and Brazil, but also reported from Switzerland, UK, USA and Saudi Arabia.[3-5]

The emergence of drug resistant (DR) strains in TB is becoming a global health concern. Patterns of resistance include *Monoresistant, Polyresistant, Multidrug resistant (MDR)* and *Extensively drug resistant* (XDR).[6]

We present here a case of a poly drug resistant TB involving the sternum. So far only few cases of Drug Resistant TB involving the sternum have been reported in literature[5, 7-10] and we were unable to find a similar case with poly drug resistant sternal TB.

Corresponding Author: Beenish Syed,
Assistant Professor, Infectious Disease Consultant
Department of Internal Medicine, Liaquat National Hospital, Karachi.
E-mail: bnishsyed@yahoo.com

Case history
66–years –old male, previously well, presented with c/o fever and significant weight loss for 1 month. He was unwell for 2 years with on and off fever, productive cough and bilateral chest pain. He was prescribed ATT, took for 10 days but discontinued by himself. There was no past history of TB or TB contact, previous hospital admission or any surgical intervention. Physical examination was completely normal except for moderate pallor.

Investigations revealed normocytic normochromic anemia with hemoglobin = 6.4g/dl, WBC=11.6, ESR=134, CRP=164, Ferritin=850, Albumin = 2.6 and ALP=427. Chest X-ray revealed mediastinal widening. (Fig 1)

CT Chest with contrast showed erosions and destruction of body of sternum with adjacent fluid collection suggestive of abscess and osteomyelitis. Multiple enlarged mediastinal, axillary and para aortic necrotic lymph nodes were noted. Erosions and soft tissue density were also seen at D8-9 vertebral body (Fig 2).

Patient remained febrile despite IV antibiotics, so open thoracatomy was done with drainage of abscess and resection of ribs and cartilage. Histopathology revealed chronic granulomatous inflammation with necrosis and Genexpert

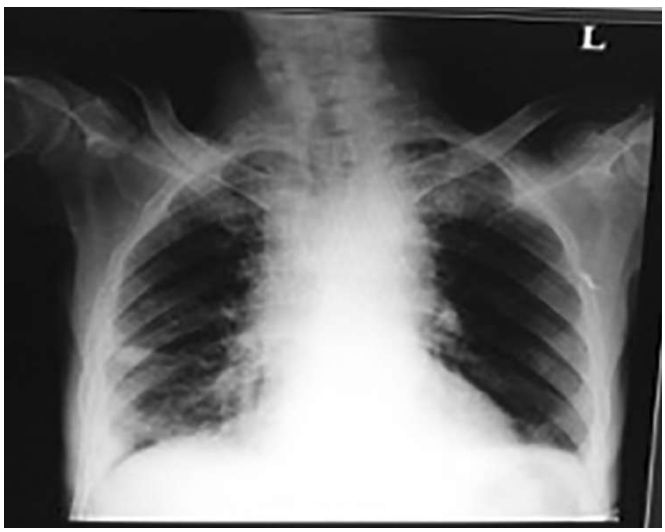

Fig 1. Chest Xray showing mediastinal widening

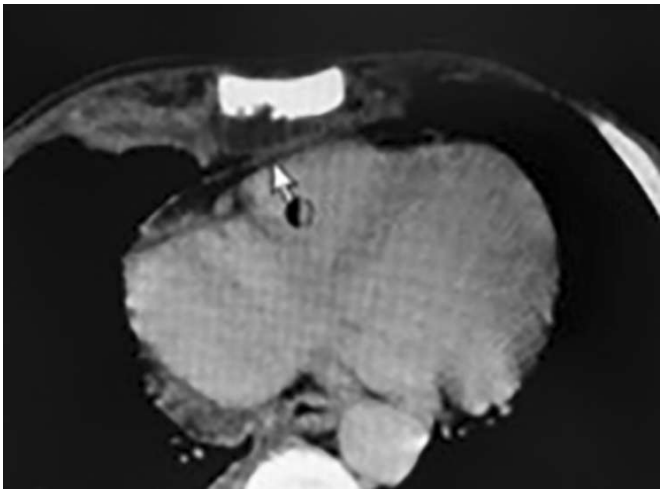

Fig 2. CT scan Chest with arrow pointing at fluid collection

(PCR) was positive for *Mycobacterium Tuberculosis* with no Rifampicin resistance detected.

Patient was started on anti tuberculous therapy with Isoniazid (H), Rifamipicin (R), Ethambutol (E) and Pyrazinamide (Z) with Pyridoxine. Patient became afebrile after 1 month but complained of generalized weakness with no significant weight gain at 2 months.

AFB CS reported resistance to Streptomycin(S) and H and sensitivity to R, E and Z, which meant that the isolate was *Polydrug resistant*. Therapy was modified to HREZ + Levofloxacin + Amikacin (for 3 months). HREZ and Levofloxacin were continued for another 7 months. ATT was stopped after 10 months of treatment and patient remained clinically stable. ESR came down to 22 and CRP to 3.5.

Discussion

Most cases of drug resistant TB involving sternum are reported from India and one from Pakistan.[5,7-11] A brief review of drug resistant Tuberculosis involving the sternum is presented in Table1. Most cases are of Multi-drug resistant (MDR) Tuberculosis from India[5,7, 9-10] and one case of Extensively drug resistant (XDR) TB of sternum was reported from Pakistan[(11)]. So far to our knowledge no case of PDR Tuberculous Sternal osteomyelitis has been reported.

Resistance to two or more first-line drugs but not to both isoniazid and rifampicin is called polydrug resistant TB. It has a global prevalence of 17% along with mono resistant TB.[1,6] Mostly remains undiagnosed as drug sensitivity testing (DST) is not routinely performed in resource limited settings, where it is seen more commonly.[1,6] It can lead to amplification of resistance (i.e. acquisition of resistance to other drugs) and MDR - TB on treatment with the standardized 1st line drugs, if remains undetected.[1-6] Therefore, performing DST using rapid tests is imperative before starting treatment.[6] Genexpet/Line Probe Assay (LPA) are rapid, sensitive and cost effective than conventional phenotypic testing.[1,6] Resistance testing to both isoniazid and rifampicin using LPA gives results within a day or two, while Xpert MTB/RIF only tests for rifampicin resistance.[1,6]

The standardized 1st line regimen of WHO has resulted in treatment failure and amplification of resistance in many studies (failure rates of 18-44%).[1, 6] Very few randomized clinical trials have been done to determine best treatment options.[(1)] At least 3 or 4, likely effective drugs should be selected.[6] DST results at baseline and previous treatment history should be considered to design the appropriate regimen.[6] Choice of drugs include combination of first and second line ATT including injectables depending on the DST results, given for duration of 9-18 months.[6] Appropriate treatment of PDR TB can prevent development of MDR – TB.[1-10]

Conclusion

Tuberculous sternal osteomyelitis, a rare entity, has to be suspected to be diagnosed. Drug resistance is emerging as a menace even in less common EPTB scenarios. Rapid tests and DST are imperative for managing drug resistant cases. As literature suggests, most cases are still responsive to second line drugs (SLDs).

Table 1: Literature review of cases with Drug Resistant Sternal TB

	No of patients	Age of patients	Gender	Symptoms	Pattern of Resistance (AFB cuture)	Duration of treatment	Surgical Debride-ment	Outcome	Treatment given
Yadav *et al* (2016)	1	21 years	F	Painful swelling on anterior chest wall	Resistant to Isoniazid, Rifampicin --- Multidrug resistant	24 months	No	Treated	Kanamycin, Levoflox, Cycloserine, Ehionamide, PAS powder and Ethambutol, Pyrazimide

Khan *et al* (2007)	2	Not specified	Not specified	Not specified	Resistant to Isoniazid, Rifampicin --- Multidrug resistant	24 months	No	Treated	Streptomycin, Ethionamide, Ofloxacin, Pyrizinamide and Ethambutol
Haseeb *et al* (2015)	1	29 years	F	Painful swelling on anterior chest wall plus fever and weight loss	Resistant to (R)- rifampicin, (H)isoniazid, (E)-ethambutol, (Eto)-ethionamide, (Ofx)-ofloxacin and (Am)-amikacin - Extensively drug resistant	5 months Stopped by patient because of adverse effects	Yes	Remained symptom free	Capreomycin, Moxifloxacin, Ethionamide, Cycloserine, PAS, Linezolid, Clarithromycin, Amoxicllin/ Clavunate, Pyrizinamide,
Mohan K *et al* (2013)	1	25 years	M	Anterior chest wall swelling with fever and weight loss	Resistant to isoniazid (INH) and rifampicin (R)	24 months	No	Treated	Kanamycin, Levofloxacin, Ethionamide, para aminosalicylic acid (PAS) and Ethambutol
Goyal S *et al* (2014) [11]	1	12years	F	Pain and swelling chest wall plus fever and weight loss	Resistant to isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S)	18 months	Yes	Treated	Kanamycin, Pyrizinamide, Ethoinamide Ofloxacillin, PAS

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Instructions to Authors

Scope
The Infectious Diseases Society of Pakistan sponsors the Infectious Disease Journal of Pakistan (IDJ). The Journal accepts Original Articles, Review Articles, Brief Reports, Case Reports, Short Communications, Letter to the Editor and Notes and News in the fields of microbiology, infectious diseases, public health; with laboratory, clinical, or epidemiological aspects.

Criteria for publication
All articles are peer reviewed by the IDSP panel of reviewers. After that the article is submitted to the Editorial Board. Authors may submit names and contact information of 2 persons who potentially could serve as unbiased and expert reviewers for their manuscript, but IDSP reserves the right of final selection.

Submission of the Manuscript
Manuscripts must be formatted according to submission guidelines given below, which are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (originally published in *N Engl J Med* 1997;336:309-15). The complete document appears at www.icmje.org. Please submit one complete copy of the manuscript and all enclosures to **The Managing Editors, Infectious Diseases Journal of Pakistan, Department of Pediatrics & Child Health, The Aga Khan University, Stadium Road, P.O. Box 3500, Karachi 74800, Pakistan.** An electronic copy of the manuscript must also be sent to pak_idj@yahoo.com**.** All manuscripts submitted to IDJP must be accompanied by an Authorship Declaration stating that *'The authors confirm that the manuscript, the title of which is given, is original and has not been submitted elsewhere. Each author acknowledges that he/she has contributed in a substantial way to the work described in the manuscript and its preparation'*. Upon submission a manuscript number will be assigned which should be used for all correspondence.

Manuscript Categories

I. Original Articles
Articles should report original work in the fields of microbiology, infectious disease or public health.The word limit for original articles is 2000.

Title page
This should list the (i) title of the article, (ii) the full names of each author with highest academic degree(s), institutional addresses and email addresses of all authors. (iii) The corresponding author should also be indicated with his/her name, address, telephone, fax number and e-mail address. (iv) A short running title of not more than 40 characters (count letters and spaces) placed at the foot end of the title page.(v) a conflict of interest statement should also be included in this section.

Abstract
Abstract should not exceed 250 words and must be structured in to separate sections headed *Background, Methods, Results and Conclusions*.

Please do not use abbreviations or cite references in the abstract. A short list of four to five key words should be provided to facilitate.

Background
The section must clearly state the background to the research and its aims. Controversies in the field should be mentioned. The key aspects of the literature should be reviewed focusing on why the study was necessary and what additional contribution will it make to the already existing knowledge in that field of study. The section should end with a very brief statement of the aims of the article.

Materials and Methods
Please provide details of subject selection (patients or experimental animals). Details must be sufficient to allow other workers to reproduce the results. The design of study and details of interventions used must be clearly described. Identify precisely all drugs and chemicals used, including generic name(s) and route(s) of administration All research carried out on humans must be in compliance with the *Helsinki Declaration*, and animal studies must follow internationally recognized guidelines. The authors are expected to include a statement to this effect in the Methods section of the manuscript. A description of the sample size calculation and statistical analysis used should be provided.

Results
Present results in logical sequences in the text, tables and illustrations. Articles can have a maximum of 5 illustrations (in a combination of figures and tables) per article. The results should be in past tense and repetition of results presented in the tables should be avoided. Exact *P*-values should be reported along with reporting of OR and RR with their Confidence Intervals where applicable.

Discussion
Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat the details from the results section. Discuss the implications of the findings and the strengths and limitations of the study. Link the conclusions with the goals of the study but avoid unqualified statements and conclusion not completely supported by your data.

Acknowledgments
Acknowledge any sources of support, in the form of grants, equipment or technical assistance. The source of funding (if any) for the study should be stated in this section. Please see below for format of **References, Figures and Tables**.

II. Review Articles
Authoritative and state of the art review articles on topical issues are also published, with a word limit of 2000. It should consist of critical overview of existing literature along with reference to new developments in that field. These should be comprehensive and fully referenced. Articles should contain an Abstract; Main Text divided into sections, Conclusions and References.

III. Brief Reports
Short clinical and laboratory observations are included as Brief Reports. The text should contain no more than 1000 words, two illustrations or tables and up to 10 references.

IV. Case Reports
Instructive cases with a message are published as case reports. Routine syndromes or rare entities without unusual or new features are invariably rejected. The text should contain no more than 1000 words, two illustrations or tables and up to 10 references. The authorship should not exceed 3-4 persons.

V. Letter to the Editor
These may relate to material published in the IDJP, topic of interest pertaining to infectious diseases, and/or unusual clinical observations. A letter should not be more than 300 words, one figure and 3-5 references.

VI. News and Views
Informative, breaking news updates in infectious diseases from around the world (approx. 200 words).

VII. Notices
Announcements of conferences, symposia or meetings may be sent for publication at least 12 weeks in advance of the meeting date. Details of programs should not be included.

References
Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals (in superscript). References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification of the particular table or illustration. Bibliography should be given in order. Authors, complete title, journal name (Abbr), year, vol, issue, page numbers. According to "Uniform Requirements of Manuscripts submitted to Biomedical Journals", as cited in N Engl J Med 1997; 336:309-15.

Tables and Figures
Data reported either in a table or in a figure should be illustrative of information reported in the text, but should not be redundant with the text. Each table must be presented on a separate sheet of paper and numbered in order of appearance in the text. Table should be numbered consecutively in Arabic numerals. Tables and Figures legends should be self-explanatory with adequate headings and footnotes.Results which can be described as short statements within the text should not be presented as figures or tables.

Illustrations
Illustrations should be numbered, given suitable legends and marked lightly on the back with the author's name and the top edge indicated. Original drawings may be submitted although high quality glossy photographs are preferable. They should be kept separate from the text. If possible, figures should be submitted in electronic format as either a TIFF (tagged image file format) or JPEG format. Minimum resolution for scanned artwork is:

- Black& white line illustration (e.g. graphs): 600 dpi
- Black & white halftone illustrations (e.g. photographs): 300 dpi
- Color illustrations: 400 dpi (note that color images should be split CMYK not RGB)

Plagiarism
Authors should refrain from plagiarism and should double check their work before submitting it for publication. Adequate references should be provided for text from other sources.

Authorship criteria
Those who have contributed sufficiently to the conceptualization, design, collection and analysis of data and writing of the manuscript should be granted authorship. Ideally all authors should be from the same department except for studies that are multi center or multispecialty.

Instructions updated - April 2012.
Editor IDJ

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