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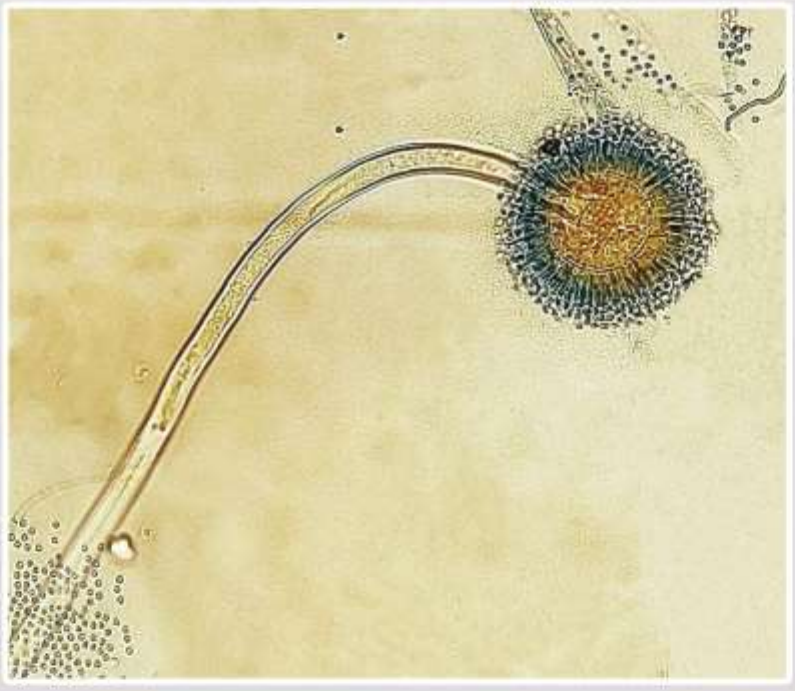

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CONTENTS

ORIGINAL ARTICLE

PERCEIVED KNOWLEDGE, ATTITUDE, AND BEHAVIOR OF PARENTS/CAREGIVERS TOWARDS ROUTINE IMMUNIZATION IN DISTRICT PISHIN, BALOCHISTAN PAKISTAN: A CROSS-SECTIONAL SURVEY

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ABSTRACT

Background: This study evaluates the perception, attitude, and behavior of parents/caregivers towards the vaccination of their child. vaccination is the greatest impactful steps, determining the real goal for public health.

Material and Methods: A cross-sectional survey was conducted among the sample of 403 Parents/caregivers of children aged under 5 years by using a two-stage random sampling technique in the period between February to March 2022 in district Pishin of Baluchistan, Pakistan.

Results: Community health workers were used to administer the questionnaire to parents or caregivers, to seek information about 1) Socio-demographic characteristics 2) knowledge regarding vaccines and their types; 3) behavior regarding the administration of vaccination. The knowledge regarding vaccine-preventable diseases was higher in parents who attend higher levels of education. HCPs were the primary source of information and the majority of sources are verbal. Parents/caregivers show a positive attitude toward vaccines and 59% are aware of vaccine importance and 39% are aware of childhood diseases with their names.

Conclusion: The positive attitude was significantly higher in those who considered vaccines boost immunity and protect against diseases. Greater attention from policymakers and healthcare providers is needed to increase the knowledge-seeking behavior of parents/caregivers on recommended vaccines and their importance on timeliness and completion to increase immunization coverage.

Keywords: Vaccine-preventable diseases, Immunization, Childhood

BACKGROUND

For primary prevention of common childhood diseases (CHD) vaccine is one of the greatest impactful steps, delineating the real goal for public health.[1] Vaccines decreased the economic and social burden linked with mortality and morbidity and eventually common childhood diseases. Vaccines are considered unsafe and needless despite knowing all these benefits in the general population.[2] Immunization activities are widely practiced in the pediatric field. American Academy of Pediatrics, provides recommendations after emphasizing the clear importance of vaccination in this age group.[3] The immunization record shows, 1.5 million children die due to vaccine-preventable diseases annually.[4] Child age under 1 year of age dies due to vaccine-preventable diseases.[5] Pakistan is still far from the objective of complete vaccine coverage.

The Expanded Programme on immunization (EPI) established in 1976, provide vaccination for six childhood diseases: tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus, and measles. If EPI is discontinued 1000 deaths in under five years of children will likely to occur.[6] Significant regional disparities, only 27% of children in Baluchistan are fully immunized. The Quetta and Qilla Abdullah are the high-risk reservoir hubs.[7] It is therefore interesting to assess the perceived knowledge of parents/caregivers regarding vaccination, as they are the primary source of information in delaying vaccination and make an informed contribution to decision making in health-related matters of family. The literature highlighted different studies assessing the knowledge, attitude, and behaviors of parents/caregivers and healthcare providers regarding vaccination,[8,9] defining specifically one vaccine-preventable disease associated with

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vaccination.[10,11] However, in Baluchistan, there is a dire need to draw attention to the issue of decreased vaccination coverage and assess the perception, attitude, and behaviors of parents/caregivers. The secondary focus of this study was to find out the determinants associated with these outcomes.

MATERIAL AND METHODS

The survey was conducted from February to March 2022 in the geographical area of district Pishin under the Quetta block, the boundary with Qilla Abdullah, Qilla Saifullah, Quetta, and Afghanistan. The population size of this area is approximately a 0.8million. District Pishin is comprised of four tehsils (Barshore, Karezat, Huramzai and Pishin). To obtain the data of 430 parents/caregivers of district Pishin two-stage cluster sampling techniques were being applied, 1) identified list of 43 union councils; 2) 10 households were selected randomly from each union council where children under five years old were present. 27 parents/caregivers refused to participate in the study and 403 parents/caregivers were recruited as per inclusion criteria, The effective sample size was estimated to be 430, 95% confidence interval, an error of 5% and non-responsiveness rate was 6.2%.

Prior to data collection the research team contacted union counselor of selected district by letter of permission to collect data, shed lights on objectives of the study, methodology, and assuring the confidentiality and privacy of participants. On secondary level is written and verbal informed consent was taken from parents/caregivers before administration of the questionnaire. Participants were informed that the collected data will be anonymously processed and analyzed and their identity will be mentioned as pseudo-number. The respondent did not receive any financial compensation to get enrolled in this study.

A standardized questionnaire was used, the first part was about the socio-demographic characteristics of participants, second part was about knowledge of vaccination, associated diseases, and recommended vaccines and the last part was about the behavior of participants on vaccine recommendation, source of knowledge, advice from health care providers and whether they need additional information. All statistical analysis was performed on Software SPSS version 18. Initially descriptive analysis has been performed to assess demographic characteristics and secondly chi-square test was conducted for bivariate analysis. Standardized linear regression analysis was performed with statistical significance level of p value <0.05.

RESULTS

A total of 403 parents responded to the cross-sectional survey with a response rate of 93.9%. The majority of the parents/caregivers who responded to questionnaire were male and mean age was 36.7 ± 4.2 years. Approximately one third have a post graduate degree. The demographic characteristics are described in Table-I. The mean age of children was 20 ± 4.2 months.

Among the 403 respondent, 67 (16%) respondents suggested the ideal age for vaccination is 0 to 6 months, age 6m to 5 years 29 (7.1%), at birth 193 (47.8%), and others have no idea 115 (28.5%). Majority of the respondent 240 (59%) stated that vaccine boost the immunity and protect from childhood diseases and the remaining 158 (39%) has a different opinion on vaccination described in Table-II.

Knowledge regarding vaccination recommended for children under five years children are mentioned in Table-III. Approximately 158 (39%) of respondents are aware of diseases prevented by vaccine administration. 256 (63.5%) of respondents perceived that one or more can be given to the child at one time and it causes no harm. 266 (66%) of the respondent received information on the side effects and benefits of vaccines through health care providers (HCPs). It was observed that the majority of the information provided verbally by HCPs and brochures were given least importance. Logistic and linear regression analysis are the significant predictors of knowledge: educational level and source of information. Those who received information from HCPs were more likely to understand the importance of vaccination (OR = 2.24; 95% CI 1.53 -6.50).

With regards to the attitude of the respondents 18 (4.4%) perceived that vaccine causes disease and kills the child and the majority of the respondents considered them safe and protects against childhood diseases. Factors such as motivation, positive attitude, and understanding of vaccine usefulness were higher among those parents/caregivers 240 (59%) who understand that vaccines are not harmful to their children. Parents perceived that if a child is vaccinated then other children in surrounding are also protected from

acquiring the CHD.

Table-I: Demographic characteristics of parents.

Characteristics	N	%
Age, mean ± SD, years	36.7 ± 4.2 (18-55)	
Gender		
Female	20	4.96
Male	383	95.0
Number of children		
1	200	49.6
2	131	32.5
3	53	13.1
4	19	4.7
Education level		
No formal education	79	19.6
Primary level	130	32.2
Secondary Level	125	31.0
Graduate	15	3.7
Post-graduate	55	13.6
Marital status		
Married	389	96.5
Widow/widower	08	1.98
Divorcee	06	1.48

Table-II: Myths and Understanding regarding vaccine

Understanding regarding vaccine	**N**	**%**
It boosts immunity and protects against childhood illness	238	59.3%
Causes disease to children and kills	18	4.4%
It's a medicine	11	2.7%
No idea	136	33.7%

Table-III: Knowledge and Understanding of Vaccine Preventable Diseases VPD.

Which disease can be prevented	**N**	**%**
Influenza	22	5.45%
Tetanus/Diphtheria/pertussis	47	11.6%
Measles/Mumps/rubella	154	38.2%
Varicella	154	38.2%
Pneumococcal disease	11	2.72%
Human papillomavirus	0	-
Meningococcal disease	160	39.7%
Hepatitis A	48	11.9%
Hemophilus influenza type b	3	0.7%

DISCUSSION

This study was conducted in the district Pishin of Baluchistan, Pakistan, the perceived knowledge, attitude, and behavior regarding vaccines among parents/caregivers and the factors linked with them. The findings of the study show unique result, found that among people attend higher degree qualifications, 59% perceived that it's not harmful. 38.2% of the respondent are aware of childhood diseases that can be prevented by vaccine administration. The refusal rate is higher in this district due to the lack of sources of information in form of brochure, pamphlet, only verbal information was provided in first place.[12-14] Female participation in this study was very low as male caregivers are decision-makers in family concern to health-related issues. It is important to underline that, regardless of the positive attitude vaccine ratio in this area is still very low and this draws the attention of policymakers and healthcare professionals working on one goal should make an effort to plan intervention and ensure full coverage despite all barriers. Similar studies were conducted regardless of low vaccination coverage in developed countries the US, Canada, and Germany.[15-17] This study as well as previous studies indicated the importance of vaccination coverage and efforts to make it 100% is essential. Another reason for low coverage we found is the cost of vaccine which creates delay in completion of immunization on time, 39.2% parents pay out of pocket cost to get their child vaccinated. Despite of the low vaccination coverage respondents showed a positive attitude towards willingness to receive the recommended vaccine. No matter how the lower rate of vaccination is several reasons pop up fear and no understanding of the side effects of vaccines, communication gap between HCPs and parents, lack of knowledge-seeking behavior.[18] To aware the parents/caregivers Healthcare workers HCWs working at the community level should be more involved, information strategies are needed to bring impactful results.

The objective of the study was to provide a basic understanding of factors associated with low coverage of vaccines. The primary source of information was HCPs, this is because people trust more on physician's advice and previous studies suggested that HCPs are the more reliable source of acquiring health-related information. It has been observed that females are less likely involved in the decision-making process, female caregivers should be involved in delivering the counseling services door to door and increase the involvement of them increase coverage response, similar studies in same geographical area suggested that providing information, knowledge, attitude, and behavior within the targeted population vaccine coverage is higher.[14, 18, 19]

This survey has a few limitations that should be considered to make a correct interpretation of findings,

recall biases are possible due to the cross-sectional survey methodology and the fact that 27 parents/caregivers refused to participate in the study may have skewed the results and limited the generalizability of the findings to other districts in Balochistan but qualitative approach may help in understanding the deep root causes of low vaccine coverage.

CONCLUSION

Decreasing immunization coverage is a major public health concern globally. It is important for children to receive their recommended doses of vaccines in a timely and complete manner in order to protect them from vaccine-preventable diseases. From the perspective of Balochistan, the educational status of the father and mother are key factors in increasing immunization coverage. This finding is consistent with similar studies that have been conducted.

To achieve the desired outcome of increased immunization coverage, it is important to conduct awareness sessions and provide counseling to parents and caregivers. Female healthcare providers can play a particularly important role in increasing female caregiver participation in immunization efforts. By involving female healthcare providers, it may be possible to increase the participation of female caregivers in the immunization process and improve overall immunization coverage in the region. Cost-effective intervention should be executed to achieve the objective.

FUNDING

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

AUTHOR CONTRIBUTION

Najeeb Ullah, Anwar Bughti: Data collection, drafted the outline

Jawwad Afzal Kayani: Data analysis and finalizing the manuscript

Farman Ullah: Data analysis

Muhammad Azan Ahmed: Writing the manuscript, Literature review

Hamd Ullah: Drafting and proofreading of the manuscript

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ORIGINAL ARTICLE

IMPACT OF ACTIVE SURVEILLANCE SCREENING OF MRSA ON SURGICAL SITE INFECTION RATES- A PROSPECTIVE INTERVENTIONAL STUDY

Tazeen Fatima, Faiza Rezwan, Farheen Ali, Shobha Luxmi, Furqan Ahmed Raheel, Muhammad Nadeem

National Institute of Cardiovascular Diseases, Karachi Pakistan

ABSTRACT

Background: Methicillin-resistant Staphylococcus aureus (MRSA) is one of the most common cause of surgical site infections. Different methods are employed to reduce nosocomial spread including application of Isolation precautions, admission screening cultures and MRSA decolonization [3,4,5,6,7]. Preoperative MRSA screening in patients undergoing cardiac surgeries can reduce the risk of surgical site infections. To evaluate the significance of preoperative MRSA screening on rates of surgical site infections in cardiac surgery patients

Material and Methods: This was a prospective interventional study, conducted at the National Institute of Cardiovascular diseases, Karachi from 1st February 2022- 31st July 2022. Preoperative MRSA screening in patients undergoing cardiac surgeries was performed at the Microbiology Laboratory. Patients identified as colonized were isolated and decolonized with chlorhexidine baths prior to surgeries. Surgical site infections (SSIs) rates were recorded by Infection control nurse through active surveillance for the screening period. SSI rates for a prescreening period of 6 months (August 2021- January 2022) was retrieved through electronic medical records for comparison.

Results: Total 359 patients were screened from 1st February 2022- 31st July 2022, out of which 20 were colonized with MRSA. None of the patients who screened positive for MRSA developed SSI. 11 SSIs with MRSA were reported from August 2021- January 2022 and 4 SSIs were reported from February 2022-July 2022 (p value < 0.05).

Conclusion: It can be concluded that active MRSA screening and subsequent implementation of decolonization policy would decrease the percentage of SSI in cardiac surgery

Keywords: MRSA, Screening, Surgical site infection, Surveillance

BACKGROUND

Staphylococcus aureus is one of the most common cause of nosocomial and health care associated infections. A significant rise in the frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) strains is seen in last few decades which is a huge challenge in management of complicated infections. With a current prevalence of more than 60% reported across the country,[1] MRSA has become the leading cause of nosocomial skin and soft tissue infections.

Surgical site infections (SSIs) are defined as those skin and soft tissue infections, developing at the surgical site within 90 days of a surgical procedure (Cardiac surgery, Coronary artery bypass graft with both chest and donor site incisions, Coronary artery bypass graft with chest incision only, Pacemaker surgery).[2] SSIs is one of the most common nosocomial infection, accounting for 14% to 25% of healthcare associated infections.[3,4] Though most cases can be prevented by following appropriate infection prevention practices but unfortunately despite the implementation of infection prevention bundles, the incidence of SSIs remains 2% to 5% in all kinds of surgeries including cardiac surgeries.[5,6,7,8] Even this figure may be an underestimation and the actual number of infections is higher, probably because most of the patients have been discharged from hospitals when SSI develops and diagnosis is missed due to poor surveillance system. The rates are even higher in underdeveloped and developing countries as compared to developed countries ranging from 2.5% to 41.9%.[9] SSI is a serious complication as it contributes significantly to increased postoperative length of hospital stay, financial burden, long-term disability, and mortality. SSIs are responsible for one third of postsurgical deaths and 8% of all deaths attributed to nosocomial infections[10] According to a meta-analysis, around 19.1% of SSIs are caused by *S.aureus*, and MRSA is the causative agent in 40% of these infections.[11]

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According to the Centre of disease control and prevention (CDC) application of contact precautions is the primary infection control procedure for reducing the nosocomial spread of MRSA.[12] Some healthcare institutes perform admission screening cultures for MRSA[13, 14, 15, 16] which is followed by contact isolation of the colonized patients and MRSA decolonization by different regimens including chlorhexidine baths, 2% intranasal mupirocin and washing with povidone-iodine soap and systemic antibiotics like oral regimens of rifampicin and doxycycline and trimethoprim-sulfamethoxazole.[17,18,19] Preoperative MRSA screening in patients undergoing cardiac surgeries and interventions can be helpful to promptly identify colonized patients, isolate and decolonize before surgery, which can later reduce the risk of surgical site infections with MRSA. Vancomycin is frequently used as a part of preoperative surgical prophylaxis in cardiac surgery especially with prosthetic material and in patients with known colonization.[6] Vancomycin is preferable when frequency of MRSA infections and colonization is high, as it can also lower the rates for SSIs.[25]

MRSA screening and subsequent decolonization of patients is an effective yet debated method considering additional interventional costs to hospitals and patients and delays in surgical schedules. Only few studies have assessed the impact of preoperative MRSA screening on rates of surgical site infections in a cardiac care hospital.[26]

Based on this background we conducted a study to determine the prevalence of MRSA in SSIs and also to evaluate the impact of preoperative MRSA screening and decolonization on rates of surgical site infections in a cardiac care hospital.

MATERIAL AND METHODS

A prospective interventional study was conducted at the National Institute of Cardiovascular diseases, a 600-bed tertiary cardiac care hospital in Karachi from 1st February 2022- 31st July 2022. All patients admitted for invasive surgeries were included in the study by Simple consecutive sampling. Patients were screened for MRSA by nasal and axillary swabs, taken on admission or in case more than 72 hours had lapsed after admission screening and surgery wasn't performed, a second nasal swab was collected 24 hours before surgery to establish nosocomial acquisition. MRSA culture and identification was performed at the Microbiology Laboratory. Patients identified to be colonized were immediately isolated in single room along with contact precautions application and chlorhexidine baths provision. Surgical site infection (SSI) rates were recorded by dedicated Infection control nurses prospectively for the screening period from February 2022-July 2022. A comparative prescreening period from August 2021- January 2022 was defined and SSIs rates was retrieved for this period from the hospital medical records.

Screening swabs were taken from both anterior nares and axilla. Identification and sensitivity testing was performed as following:

Both swabs were inoculated in enrichment broth for two hours and later broth was sub cultured onto blood agar plate, incubated at 35°C for 24-48 hours and examined for 48 hours. Suspected colonies were identified by standard procedures (Gram staining, catalase test, tube and slide coagulase test, DNAse test and fermentation of mannitol). Once identified as Staphylococcus aureus, resistance to oxacillin was determined via the cefoxitin disk diffusion method (zone of inhibition was ≤21 mm) (BD, Oxoid, UK) according to Clinical and Laboratory Standards Institute (CLSI) recommendations.

RESULTS

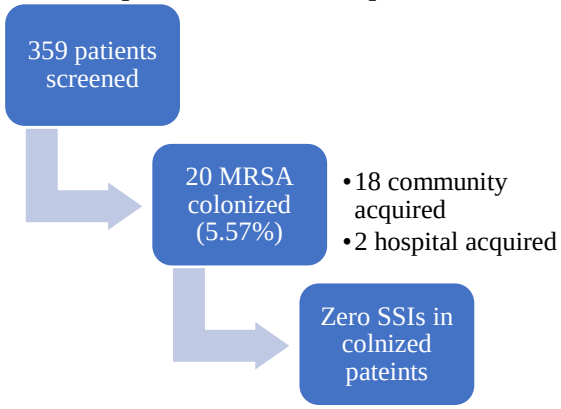
Preoperative MRSA screening was performed for total 359 patients from February- July 2022, admitted for different kinds of cardiac surgeries including Coronary artery bypass surgery (CABG), Intra-aortic balloon pump (IABP), Mitral valve replacement (MVR), Atrial septal defect (ASD) repair, Modified bental procedure, Transcatheter aortic valve replacement (TVR) Aortic valve replacement (AVR), Aortic grafting, Patent ductus arteriosus (PDA) closure, Ruptured sinus of valsalva aneurysm (RSOV) repair etc.

Among the 359 screened patients, only 20 were colonized with MRSA (5.57%). 18 of the patients had MRSA colonization on admission which can be attributed to community acquisition, and only 2 had MRSA identified after 72 hours of admission which can be recognized as nosocomial acquisition. However. No SSIs were recorded in any of these colonized patients within 90 days of surgery.

During these 6 months, 4 MRSA SSIs were recorded but none of these patients had evidence of colonization

on initial screening. A 6-month prescreening period was identified from August 2021- January 2022 for comparison of SSI rates, and 11 SSIs were reported during that period. Using Fischer exact the difference between the SSI rates in these two periods was found to be significant (p value < 0.05) Figure-I.

Figure-I: Breakup of MRSA colonised patients.



DISCUSSION

MRSA is a notorious and highly adaptable bacterial pathogen with high virulence and antibiotic resistance. It is considered to be the commonest cause of nosocomial infections, especially SSIs. Poor infection prevention measures, excessive use of unwarranted broad -spectrum antibiotics producing selection pressure, and cross-transmission through healthcare workers' hands, facilitates its spread. Hence, early identification and preemptive decolonization might decrease infections as MRSA carriers are main pathogen reservoirs.[21,22]

The dramatic increase in incidence of MRSA strains is associated with adverse clinical and monetary effects. There is an excessive use of anti-MRSA agents such as vancomycin as empirical as well as targeted therapy, even in the absence of proven MRSA infections due to high MRSA burden in community and hospitals.[23] A study quoted an experience of vancomycin overuse, over a three-year period in a Boston hospital, according to which 2910 patients received at least one dose of vancomycin during their hospital admission, while only 195 (6.7%) had actual MRSA infection[24]. Vancomycin on one hand is associated with important adverse effects like acute kidney injury, red man syndrome, and on the other contributes to rising antimicrobial resistance especially increasing rates of vancomycin resistant enterococci. In addition to these, the burden of drug level monitoring cost and the drug cost itself is humongous.

Preoperative MRSA screening is safe and cost-effective adjuvant approach to control the postoperative rates of MRSA infections. Early detection of MRSA colonization, decolonization, cohorting or isolation, can prevent cross-transmission between patients and also to healthcare workers. Even though the cost effectiveness of screening has been debated, positive colonization status of a patient can help decide empiric MRSA therapy[23,24] in cases of presumed *Staphylococcus aureus* bacteremia or reserve therapy in case of negative colonization status. Vancomycin is a frequently used drug as a part of preoperative surgical prophylaxis especially in cardiac surgery with prosthetic material, in patients with known MRSA colonization and in areas with high prevalence of MRSA infections.[25] However, preoperative MRSA screening can help identify the true burden and prevalence, which can help devise surgical prophylaxis guidelines and revisit the compulsion of including vancomycin in surgical prophylaxis.

CONCLUSION

This study showed a substantial decrease in MRSA SSIs after the commencement of screening protocol and it can be concluded that active MRSA screening and subsequent implementation of decolonization policy would decrease the percentage of SSI in cardiac surgery.

LIMITATIONS

One of the limitations of this study is the absence of post-decolonization screening results, which could have helped evaluate the efficacy of decolonization protocol. Another limitation is the smaller sample size and duration of study. Larger prospective studies are required to confirm these results.

FUNDING

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

AUTHOR CONTRIBUTION

Tazeen Fatima: Conception, design, execution, analysis and drafting

Faiza Rezwan: Manuscript approval

Farheen Ali, Shobha Luxmi: Design, manuscript approval

Furqan Ahmed Raheel, Muhammad Nadeem: Supervision, manuscript approval

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ORIGINAL ARTICLE

CLINICAL CHARACTERISTICS AND OUTCOME OF VENTILATOR ASSOCIATED PNEUMONIA IN PATIENTS WITH RENAL FAILURE

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ABSTRACT

Background: Ventilator associated pneumonia (VAP) causes significant morbidity and mortality. Data from patients with preexisting renal failure is limited. Our aim was to evaluate the clinical characteristics and outcome of VAP in patients with renal failure and/or on maintenance hemodialysis.

Material and Methods: A prospective observational study was conducted from February 2022 to February 2023. Patients ≥18 years, on mechanical ventilation (MV) for ≥48 hours, having underlying deranged renal function and who developed VAP were included. Demographics, cause of intubation, day of onset of VAP, clinical features, laboratory parameters and tracheal cultures were noted. Patients were followed till day 14 of VAP for mortality.

Results: Out of 165 MV patients, 67 (40.60%) developed VAP, 33 (49.25%) in ≤ 4 days. The cause of intubation was respiratory distress in 58(86.8%) patients. In 61(91%) patients tracheal cultures were positive with *Acinetobacter species* (64%) as the most common organism and 93% of which were carbapenem resistant. Carbapenem resistant organisms were more frequently in case of late onset VAP (91.2% versus 72.7% p=0.049). A total of 42 patients (62%) died, 76 % within 7 days of VAP and 13 patients (19.40%) recovered with successful extubation. There was no significant difference in 14 days mortality between early or late VAP.

Conclusion: VAP rates in patients with preexisting renal failure were 40%. Half of them developed in <4 days. *Acinetobacter* spp. was the predominant causative agent. Attributed mortality was high at 63% where two thirds of patients died within 14 days.

Keywords: Outcome, Renal failure, Ventilator associated pneumonia, Mechanical ventilator

BACKGROUND

Ventilator associated pneumonia (VAP) is defined as pneumonia that develops 48hours or longer after mechanical ventilation. VAP is classified further into two types, early onset VAP that occur within 4 days of ventilation, and late onset VAP that occur more than 4 days of initiation of mechanical ventilation.[1] VAP was found to be one of the most common hospital acquired and device associated infection according to a multistate point prevalence survey conducted in United States.[2] There is a significant morbidity and mortality associated with VAP. The 2016 clinical guidelines by Infectious Diseases society of America (IDSA) reported mortality rate of up to 30-50 %.[3] A study from France showed a significant morbidity with longer ventilator and hospital stay.[4] The incidence of VAP in Europe is between 5% to 60% and in US the incidence is 2-6 episodes per 1000 ventilator days.[5] A meta-analysis from China pointed out the cumulative incidence of VAP to be 23.8%.[1] In Pakistan the incidence of VAP was reported to be around 30% with a high mortality of 60%.[6,7] Zubair *et al* did a study on elderly population and found a significant high mortality among those who developed VAP.[8] The most common risk factors linked with VAP are advanced age, male gender, prolonged mechanical ventilation, patients with altered level of consciousness, burns, chronic diseases like chronic kidney disease, prior antibiotic therapy, invasive procedures like tracheostomy, fiber optic bronchoscopy, indwelling gastric tubes and thoracic tubes.[1,7]

Pneumonia in patients with renal failure is associated with increased hospitalization, and

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mortality.[9] The risk of pneumonia in chronic kidney disease is 1.97 times higher than in the general population.[10] A systemic review and meta-analysis reported that the mortality risk is doubled in patients with kidney disease having pneumonia.[11] Data on VAP among patients with renal failure is limited. Sindh Institute of Urology and Transplantation mainly caters to patients with renal failure. Our aim is to evaluate the incidence, risk factors and outcome of VAP in patients with renal failure and those on maintenance hemodialysis.

MATERIAL AND METHODS

We conducted a prospective observational study from February 2022 to February 2023. All patients ≥18 years of age, requiring mechanical ventilation (MV) for ≥48 hours and having deranged renal function (estimated glomerular filtration rate eGFR <60ml/min) and who developed VAP (defined below) were included. Patients who were diagnosed as pneumonia before MV and transplant recipients were excluded. Patient's demographics, comorbid conditions, cause of intubation, clinical features, laboratory parameters and tracheal cultures were noted at the time of diagnosis of VAP. Patients were followed till day 14 of VAP, whether alive and extubated, alive and intubated or died, whichever came first. The study was approved by institutional ethical review board for publication.

Ventilator associated pneumonia: Pneumonia diagnosed >48 hours after endotracheal intubation characterized by new lung infiltrates on chest X ray plus the new onset of fever, purulent sputum/tracheal secretions, leukocytosis, and decline in oxygenation. [12]

Early VAP is defined as pneumonia developed <4 days, while late onset was >4 days of intubation.[1]

End Stage Renal Disease (ESRD) diagnosed by nephrologists and defined as irreversible decline in kidney function with an estimated glomerular filtration rate less than 15 mL per minute per 1.73 m^2 body surface area, or those requiring dialysis irrespective of glomerular filtration rate.[13]

Acute renal failure diagnosed by nephrologists and defined as any of the following: increase in serum creatinine by ≥0.3 mg/dl within 48 hours; or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours.[14]

SPSS version 20 was used to analyze the data. Normally distributed continues variables were be reported as mean ± SD and non-normally distributed were reported as median with interquartile range [11]. To compare the mean difference between groups, for continues variables two sample t test was used whereas chi square, independent test or fisher exact test were used to determine proportion difference between groups. A cut off value of <0.05 was determined as statistically significant difference. Based on previous estimate of VAP as 30 % (7) with a margin of error 7% and 95% confidence level, a total of 164 patients were needed for this study.

RESULTS

Out of 165 patients on MV, 67 (40.60%) were diagnosed with VAP. Table-1 shows their demographics and clinical characteristics. A total of 33patients (49.25%) developed VAP ≤ 4 days and 54 patients (80.59%) within 7 days of MV. The median age of the study population was 35 years, 25 (37.3%) were females. The cause of intubation was respiratory distress in 58 (86.8%) patients in our cohort.

Respiratory culture results were obtained in 61 (91%) patients. The most common pathogen isolated was *Acinetobacter species* (64%). In addition, 55 of 59 (93%) isolates of gram-negative bacteria were carbapenem resistant. A total of 14 (20.8%) patients had concomitant bacteremia pre and post intubation. The source of bacteremia was central line infection in 8 cases (57%), urinary tract infection in 2 cases (14%) and unknown origin in 4

cases (28.5%). None of the bacteremia was attributable to VAP.

A total of 42 (62%) patients died. Thirty-two (76.19%) died in <7 days of VAP diagnosis. A total of 13 (19.40%) were alive with successful extubation.

The comparison of early and late onset VAP is shown in Table-2. Male patients developed VAP early compared to females, however did not reached statistically significant difference. Episodes of fever were seen more frequently in patients who developed VAP after 4 days (p value= 0.035), in contrast, mean TLC was high in early than in late VAP (19% vs 14.8 % p=0.06). Carbapenem resistant gram-negative bacteria were more frequently isolated from patients suffering from late onset VAP (91.2% versus 72.7% p value=0.049). There was no significant difference in 14 days mortality between early or late onset VAP.

Table-1: Demographics and baseline characteristics of patients with ventilator associated pneumonia (n=67).

Characteristics	n (%)
Age median (IQR)	35 (25-50)
≤30 years	27 (40.3)
30-50 years	24 (35.8)
>50 years	16 (23.9)
Female	25 (37.3)
Recent hospitalization within one month	25 (37.3)
Duration of hospitalization before intubation median (IQR)	1(0-3)
Duration of intubation before VAP days median (IQR)	5.0 (3.0-7.0)
Early VAP (≤4 days)	33 (49.25)
Late VAP (>4 days)	34 (50.74)
Clinical presentation at the time of intubation	
Pulmonary edema	24 (35.8)
Advanced uremia	6 (9)
Sepsis	23 (34.32)
Seizures	6 (9)
Others	19 (28.35)
Cause of intubation	
Respiratory distress	58 (86.8)
Low Glasgow coma scale	4 (6)
Cardio-pulmonary resuscitation	11 (16.6)
Arrhythmias or cardiac arrest	13 (19.4)
Others	5 (7.5)
Renal failure types	
Acute renal failure	31 (46.26)
Acute on chronic renal failure	19 (28.35)
End stage renal disease	11 (16.41)
Comorbidities	
Diabetes mellitus	15 (22.4)
Chronic lung diseases	2 (3)
Immunocompromised	9 (13.4)
Ischemic heart diseases	1 (1.5)
Stroke	2 (3)
Laboratory parameters	
Leucocytosis	46 (68.7)
Leucopenia	5 (7.5)
Thrombocytopenia	44 (65.7)
Microbiology characteristics	
Respiratory culture isolated	61 (91.04)
Acinetobacter spp.	43(64.17)
Klebsiella spp.	12 (17.91)
Pseudomonas aeruginosa	3 (4.47)

MRSA	2 (2.98)
Carbapenem resistant gram-negative bacteria	55/59 (93.22)
Bacteremia not attributable to VAP	14 (20.89)
Before intubation (n=6)	6/14 (42.85)
After intubation (n=8)	8/14 (57.14)
Outcome at day 14 of VAP	
Death	42 (62.68)
Within 7 days	32 (76.19)
After 7 days	10 (23.80)
Alive and intubated	12 (17.91)
Alive and extubated	13 (19.40)

Table-2: Comparison between early vs late onset VAP.

Characteristics	**Early VAP (≤4 days) n=33**	**Late VAP (>4 days) n=34**	**P-value**
Age median (IQR)	40(26-56)	35(25-45.75)	0.551
Male	24(72.7)	18(52.9)	0.094
Recent hospitalization	12(36.4)	13(38.2)	0.874
Days of hospitalization before intubation median (IQR)	1(0-4)	0(0-3)	0.704
Cause of intubation			
Respiratory arrest	30(90.9)	30(82.4)	0.253
Coma	2(6.1)	2(5.9)	0.975
CPR	3(9.1)	8(23.5)	0.111
Cardiac arrest	8(24.2)	5(14.7)	0.324
Comorbidities			
Diabetes mellitus	9(27.3)	6(17.6)	0.345
Acute Renal Failure	13(39.4)	18(52.9)	0.266
Acute on Chronic Renal Failure	11(33.3)	8(23.5)	0.373
End stage renal disease	6(18.2)	5(14.7)	0.701
Bacteremia unrelated to VAP	5(15.2)	9(26.5)	0.255
Clinical parameters			
Fever	16(48.5)	25(73.5)	0.035
TLC mean± SD	19.11±9.37	14.88±8.79	0.06
Thrombocytopenia	20(60.6)	24(70.6)	0.390
Respiratory culture isolates			
Acinetobacter spp.	20(60.6)	23(67.6)	
Klebsiella spp.	5(15.2)	7(20.6)	
Morganella Morganii	1(3)	0	0.396
MRSA	1(3)	1(2.9)	
Pseudomonas aeruginosa	1(3)	2(5.9)	
Carbapenem resistant organisms	24(72.7)	31(91.2)	0.049
Mortality	22(66.7)	20(58.8)	0.507

DISCUSSION

Ventilator associated pneumonia is one of the most common complication of mechanical ventilation and renal dysfunction is a major risk factor.[1,15] We found a very high rate of VAP (around 40%) in our cohort of patients with renal dysfunction. Furthermore, half of our patients developed VAP in less than 4 days of intubation. Cook *et al* reported the risk of development of VAP was higher in 5 days as compared to10 days of MV (3%/day vs 1%/day).[16] A study from Thailand have shown higher MDR organisms, length of hospital stay, mechanical ventilation and mortality in late onset VAP as compared to early onset VAP. [17] In contrast late onset VAP was found to have high morbidity and mortality due prolonged hospital stay and multiple comorbidities.[15] However in our study there was no difference in mortality between early and late onset VAP. Hosamirudsari *et al* in a retrospective study showed similar results with no risk difference of mortality in terms of early and late VAP.[18]

We found a very high mortality of 63% where two third of our patients died within 7 days of diagnosis. Overall

both crude and attributable mortality of VAP has been reported to be around 30-50%. [15,19] A study from Pakistan in trauma related mechanically ventilated patients showed a mortality of 65.8%.[7] There is scanty data on the outcome of VAP in patients with preexisting renal disease or those on maintenance hemodialysis. Data of all types of pneumonia in patients with kidney diseases reported a two times higher mortality.[20] Chronic kidney disease is prevalent in South Asia with alarming numbers in Pakistan (23.3%) involving both younger and older population due to diabetes mellitus and renal stone disease.[21,22] CKD patients have higher burden of comorbidities and require more frequent interaction with critical care leading to increased mortality.[23] In this study, we noticed pulmonary edema and sepsis as leading cause of intubation.

The microbiology of respiratory isolates of our patients is similar as reported in literature with predominance of gram-negative organisms and Acinetobacter *spp* as the most common pathogen isolated.[17,24] In addition, carbapenem resistance was seen significantly more seen in patients with late onset VAP. This is in agreement with various studies where late onset VAP was found to be due to multidrug resistant organisms (MDR).[17,25] The reason being prolonged hospitalization may lead to colonization of hospital acquired resistant organisms leading to infection with resistant bugs Studies have shown antibiotics exposure in preceding 90 days, hospital stay >5 days, mechanical ventilation and immunocompromised patients are the risk factors for colonization and infection with MDR organisms.[18] Patients with CKD or on renal replacement therapy are also colonized with drug resistant bacteria due to frequent exposure to healthcare setting and repeated admissions.[23]

During ICU stay, patients with renal dysfunction are more prone to develop blood stream infection due to usage of indwelling access catheter and arteriovenous fistula for hemodialysis.[23] In our cohort, we found nearly one fourth of our patients developed blood stream infection prior to or after development of VAP mostly originating from central line. Basseti *et al* reported 15% of patients with VAP develop bacteremia and it is the second most important source of blood stream infection in critically ill patients.[26] Baber *et al* from our institute also found 6.8% of patients had bacteremia caused by pneumonia.[27] However we did not find bacteremia attributed to VAP in our cohort.

Conclusion: In conclusion, this is the first reported data from Pakistan on clinical features and outcome of VAP in patients with preexisting renal disease. Our cohort of renal failure patients were young, intubated due to pulmonary edema, 40% of them developed VAP, more than half in less than 4 days. *Acinetobacter* spp. remained the predominant causative agent and two third of patients died within 14 days of VAP.

LIMITATIONS

There are several limitations. This was a single center observational study with a small sample size. Inclusion of all ventilated patients with or without VAP for comparison is needed for risk factors assessment.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

AUTHOR CONTRIBUTION:

Muhammad Hassan, Zaheer Udin Babar: Contributed to manuscript writing, study methodology, data analysis.

Sanjay Kumar, Muhammad Kashif Farooq: Involved in data collection, results analysis

Sunil Kumar Dodani, Asma Nasim: Contributed in conceptualization, final manuscript writing, and results analysis.

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ORIGINAL ARTICLE

CHLAMYDIA TRACHOMATIS INFECTION IN PELVIC INFLAMMATORY DISEASE PATIENTS – A SNAP SHOT

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ABSTRACT

Background: *Chlamydia trachomatis* is a sexually transmitted infection which due to its asymptomatic nature remains undiagnosed and presents as pelvic inflammatory disease in females. The objective of the study is to find prevalence and risk factors associated with positive testing of *Chlamydia trachomatis* infection in women suffering from pelvic inflammatory disease visiting a tertiary care hospital in Pakistan.

Material and Methods: This cross-sectional study was carried out at Department of Microbiology, Army Medical College/ National University of Medical Sciences from March 2019 to September 2019. This cross-sectional study was conducted among women presenting with pelvic inflammatory disease over a period of seven months. Socio-demographic and behavioral data were collected and real-time PCR diagnostic method was used to detect the presence of *Chlamydia trachomatis* infection in urine samples. Samples were collected by non-probability convenient sampling technique; Samples were analyzed for risk factors identification and association with *Chlamydia trachomatis* infection was determined.

Results: The prevalence of *Chlamydia trachomatis* was 12 (20%) out of total 60 participants. Maximum positive cases were seen in 20-24 years of age group. Risk factors i.e., age, number of sexual partners, gross monthly income, level of education, place of residence and past sexual history were evaluated. Positive association p =0.046 was found between number of sexual partners and *Chlamydia trachomatis* infection.

Conclusion: *Chlamydia trachomatis* a sexually transmitted infection is deadly infection because of its wide range of complications. Therefore, it should be diagnosed promptly and treated effectively. Due to its asymptomatic nature individuals having risk factors should be screened as early possible to avoid complications. Information about *Chalamydia trachomatis* risk factors and education about how to avoid infection should be given to individuals on large scale.

Keywords: *Chlamydia trachomatis*, Pelvic inflammatory disease, Polymerase chain reaction

BACKGROUND

Sexually transmitted infections (STIs) is a multiple faceted public health problem having consequences on health care systems globally.(1) STIs directly affect the health of individual and indirectly effect health care system due to economic liability they cause the health care system.[2] According to World Health Organization (WHO) 2018 report nearly 350 million individuals get infected with sexually transmitted infection every year of which seven percent cases of *Chlamydia trachomatis* infection are reported.[3]

Chlamydia trachomatis presents as diagnostic dilemma due to its asymptomatic nature and remains undetected in 60 -70 percent of cases.[4] Patient presents to clinics when complications have developed and its uncontrolled transmission in community has occurred. Complications like pelvic inflammatory disease is common in females which is considered fatal as it effects mainly younger population and lead to infertility, ectopic pregnancy and death.[5] Infection with *Chlamydia trachomatis* increases the risk of being co infected with other STIs also.[6] This problem is more significant in South East Asia especially Pakistan where most cases are not diagnosed timely due to non-availability of diagnostic services, lack of awareness about safe sexual practices and social constraints. Therefore the need of hour is to conduct proper screening at Government level in resource limited countries and to create awareness about safe sexual

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practices among general public and to identify at risk populations to reduce the spread of *Chlamydia trachomatis* infection and long term consequences associated with it.[7,8]

The main objective of our study was to identify and stratify risk factors associated with *Chlamydia trachomatis* infection in women suffering from pelvic inflammatory disease visiting a tertiary care hospital.[9] In our study we performed polymerase chain reaction on urine specimen due to its noninvasive nature instead of endocervical swab which is routinely done. This method can be used as screening tool on larger scale as it requires noninvasive specimen collection technique, is a cost effective method and requires less expertise.[10, 11]

MATERIAL AND METHODS

This cross-sectional observational study was carried out at the Department of Microbiology, Army Medical College (National University of Medical Sciences), Pak Emirates Military hospital from March 2019 to September 2019 after obtaining ethical approval from institutional review board of institute.

Sixty females diagnosed with pelvic inflammatory disease were included in the study over a period of seven months after obtaining consent and confidentiality of participants were maintained at all times. Sample size was calculated by using the WHO calculator for sample size calculation by keeping Anticipated population proportion of 0.04 and confidence level of 95% (8) Inclusion criteria included all sexually active females between age of 16-49 years presenting with pelvic inflammatory disease. Males were excluded from the study as screening for males is not recommended. Females with other co-morbidities and who have already received treatment and duplicate samples from the same patient were excluded from the study.

For the purpose of this study, we defined Pelvic inflammatory disease as a clinical spectrum compromising of endometritis, salpingitis, tubo-ovarian abscess or pelvic peritonitis which was assessed through history of severe lower abdominal pain, dysuria, dyspareunia, fever, intermenstrual bleeding and prolonged menstrual cycle. We used imaging modalities to demonstrate the presence of tubo-ovarian abscess or thickened tubes with or without free pelvic fluid.

A total of sixty urine samples were collected from sixty female participants who fulfilled the study criteria and were tested for *Chlamydia trachomatis* using polymerase chain reaction assay. Urine samples were collected following aseptic guidelines and transported to laboratory in one hour otherwise specimen was stored at 2-8ºC. Specimens were stored at – 20 till tested for *Chlamydia trachomatis.* Once sample was received in laboratory 10 ml of urine was centrifuged at 1680g for 20 minutes. The supernatant was discarded, pellet processed according to manufacturer's instructions.

DNA extraction was done manually DNA was extracted from each urine sample using Pure Link Micro biome DNA purification kit Cat A29790 M/s Invitrogen, a commercially available kit. Real time PCR was done which amplified the target sequence of *Chlamydia trachomatis* cryptic plasmid gene a 71 bp DNA using a forward's primer and a reverse primer (5'–CATGAAAACTCGTTCCGAAATAGAA-3), (5'TC AGAGCTTTACCTAACAACGCATA-3') respectively following manufacturers guidelines. Instrument used was Smart cycler by Cepheid PCR system 16 well system. DNA was extracted from 200 µl thawed or from 200 µl aliquot of pellet from 10 ml of centrifuged urine.

Socio-demographic and behavioral data were collected and real-time PCR diagnostic method was used to detect the presence of *Chlamydia trachomatis* infection in urine samples. Samples were analyzed for risk factors identification and association with *Chlamydia trachomatis* infection using Statistical Package for the Social Sciences (SPSS) Version – 24.

RESULTS

Sixty female participants who fulfilled the study criteria were enrolled in the study. Frequency of *Chlamydia trachomatis* in urine specimen of this high-risk population was found to be twelve (20 percent) remaining forty-eight (80 percent) were negative for *Chlamydia trachomatis*.

Age was main factor which played a role in acquisition of *Chlamydia trachomatis* infection with maximum number of individuals in age group 20-24 being affected followed by 25- 29 years age group as shown

in Table-I. Participant's age ranged from 16- 40 years with mean age of 24.38 ± 4.85 years. Youngest participant was 16 years with oldest being 40 years.

Several risk factors were evaluated age, level of education, socioeconomic status, life time number of sexual partners, marital status, place of residence either urban or rural and past sexual history as shown in Table-I.

Socioeconomic level a major risk factor for acquiring *Chlamydia trachomatis* infection was evaluated as shown by table I. We grouped participants according to socioeconomic level. We stratified the study population as high, middle and lower socioeconomic level according to general gross income statistics of country. Around 54 (90%) subjects with low socioeconomic status while 5 (8.3%) subjects belonged to middle class and 1 (1.7%) of subjects were categorized as having upper middle socioeconomic status. Out of 12 positive subjects 10 (83.3 %) belonged to low socioeconomic status, 1 (8.3 %) belonged to middle socioeconomic status and 1 (8.3%) belonged to higher middle socioeconomic status as shown by Figure-1.

Table-I: Different factors affecting acquisition of *Chlamydia trachomatis* infection.

Age (range)	**16 -40 years**	
Age Groups in Years	**Positive n (%)**	**Negative n (%)**
15-19	2 (28.5)	5 (71.5)
20-24	5 (33)	10 (67)
25-29	4 (21)	15 (79)
30-34	nil	5 (100)
35-40	nil	4 (100)
40-44	1 (20)	4 (80)
45-49	nil	nil
Education		
Grade 5 or less than grade 5 (Elementary School)	5 (38.5)	8 (61.5)
Grade 5- Grade 8 (Middle School)	2 (11.7)	15 (88.3)
Grade 8- Grade 10 (High School)	4 (28.5)	10(71.4)
Grade 10- grade 12 (College)	1 (9.1)	10 (90.1)
More than grade 12 (Masters / University)	-	5 (100)
Socioeconomic Status (On basis of gross income)		
Lower income group	10 (18.5)	44 (81.5)
Middle income group	1 (20)	4 (80)
High income group	1 (100)	nil
Marital Status		
Married	12 (20)	48 (80)
Unmarried, divorced or widowed	-	-
No of life time sexual partners		
1	11 (20.4)	43 (79.6)
2	1 (16.5)	5 (83.5)
More than 2	-	-
Past STI History		
Present	7 (100)	-
Absent	5 (9.4)	48 (90.5)
Place of living		
Urban	10 (20)	40 (80)
Rural	2 (20)	8 (80)

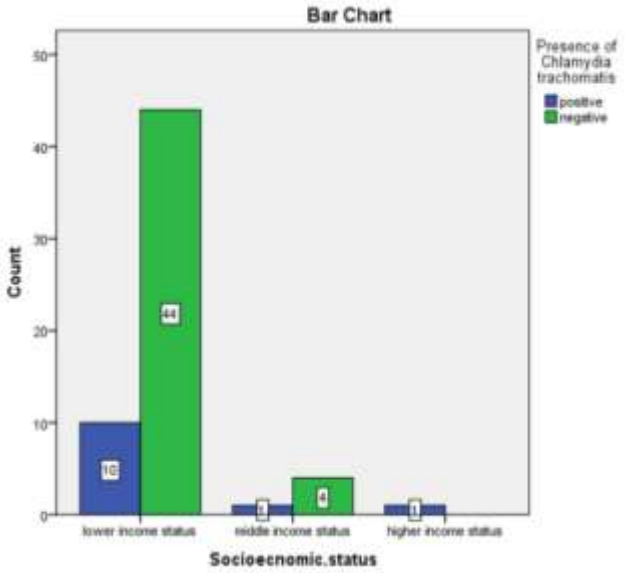

Figure-I: Frequency of *Chlamydia trachomatis* distribution among study participants according to socioeconomic status.

DISCUSSION

STIs effect not only the individuals health but also place economic burden not only on individual but also effect health care system of the country in particular and society in general by causing its uncontrolled transmission if not detected and treated in time. *Chlamydia trachomatis* is one of the most frequently occurring and easily treated STI worldwide. Around 131 million estimated cases of *Chlamydia trachomatis* occur annually raising global concern about its public health importance.[13,14]

Asymptomatic nature of infection makes diagnosis of *Chlamydia trachomatis* difficult. A study conducted at Karachi showed the prevalence to be 14.49 percent in symptomatic cases and 11.9 percent in asymptomatic persons[15] PID is the most commonly associated with *Chlamydia trachomatis* infection as a complication of its asymptomatic nature which can cause ectopic pregnancy which has significant mortality and morbidity.[16,17] It is responsible for 5-10 percent of all maternal deaths.[18]

A lot of research effort is taking place worldwide to assess risk factors associated with *Chlamydia trachomatis* infection so as to screen high risk groups early and to prevent its progression and further transmission. In Pakistan, however not much data is available that deals with *Chlamydia trachomatis* risk factor association. High risk sexual behaviours in our study was only studied in females who were heterosexuals so we could not evaluate these like male having sex with males, bisexual all these factors predispose to Chlamydial infection[19] 8.3 percent of Chlamydia positive females had more than one life time sexual partner. In our study positive association was found between no of sexual partners and diagnosis of *Chlamydia trachomatis* which correlates with international studies.[20]

In our study 20- 24 years age group was mainly affected which is consistent with other studies carried out in south east Asia.[21] A study carried out in Malaysia having similar socio demographic similarities as Pakistan showed infection was common in younger age group mainly under the age of 28 years.[22] The mean age of females infected by *Chlamydia trachomatis* was 24.38 years consistent with other studies on same subject. High risk groups are screened regularly in developed countries same should be done in Pakistan.[23] Screening should be compulsory for individual in age group from 20 to 30 years.

World over infection and complications occur more in socially disadvantaged population due to lack of knowledge about disease and accessibility to diagnosis and treatment. In our study maximum cases were seen in females belonging to disadvantaged socioeconomic status and education similar to studies carried out in Europe , North America and Australia.[24,25] There was no significant association found between education in our study mainly because major proportion of our population belonged to socially disadvantaged background as our hospital mainly caters for people belonging to lower socioeconomic status so a significant comparison cannot be done.

CONCLUSION

Due to asymptomatic nature of *Chlamydia trachomatis* infection, its ability to develop wide variety of complications high risk individuals should be identified and treated as soon as possible. Education about prevalence, risk factors and safe sexual practices should be made freely available to high-risk population.

LIMITATIONS

The main limitation of our study is it has small sample size, and is a single Centre study. A similar multi centre-based study on large scale should be carried out to determine the risk factors associated with *Chlamydia trachomatis* infection in our population.

RECOMMENDATIONS

Prevalence of *Chlamydia trachomatis* and its risk factors data is scarcely available from Pakistan, low economic status of majority of population and being a densely populated country Pakistan is high risk country

for it. Although our study was conducted for eighth months at a tertiary care hospital in one of the largest cities of Pakistan still a multicentre cohort study on larger scale should be carried out to identify risk factors.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

AUTHOR CONTRIBUTION

Afnan Naeem: Principal investigator
Hafsa Waseem: Data collection
Sakhawat Ali: Review of study
Javaid Usman: Conception of idea and study design
Faisal Hanif: Review of study
Warda Furqan: Statistical analysis

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ORIGINAL ARTICLE

ASSOCIATION OF COMMUNITY-ACQUIRED PNEUMONIA (CAP) WITH INHALED CORTICOSTEROIDS (ICS) AMONG PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Chronic obstructive pulmonary disease has a significant morbidity burden and adversely affects patient quality of life. According to research, inhaling steroids may raise the chance of developing community-acquired pneumonia (CAP). Since no research had been done in our local community, this study was conducted to determine the relationship between pneumonia and COPD patients. To determine the association of community-acquired pneumonia with inhaled corticosteroids among patients with chronic obstructive pulmonary disease (COPD).

Material and Methods: In a cross-sectional study carried out between October 15, 2020, to April 14, 2022 (18 months) at Nishtar Hospital Multan, 300 COPD patients from the Department of Medicine and Pulmonology were selected after permission from concerned authorities and the Institutional Review Board (IRB). Once registered, all patients underwent clinical examination and chest X-Ray to diagnose pneumonia.

Results: Out of these 300 research cases, our study's patients had an average age of 56.63 ±3.4 years. Out of them, 190 (63.3%) were male patients and 110(27.7%) were female. One hundred and fifty-five (51%) were from metropolitan regions, while 145 (48.3%) were from rural areas. 123 (41.0 percent) of the subjects had diabetes, and 117 (39%) had hypertension. Of these 300 study cases, 200 (66.6 %) were smokers, while dyslipidemia was noted in 136 (45.3 %). Among 300 patients, 247 (82.3%) were on ICS. Community-acquired pneumonia was noted in 43 cases (14.3%). There was a statistically significant association between ICS usage and CAP ($P<0.05$). Post-stratification, CAP had a significant association (p-value ≤ 0.05) with older age (>55 years), urban population, diabetes, smoking, and COPD duration of > 12 months.

Conclusion: Our study noted a high CAP prevalence among COPD patients using ICS. Moreover, community-acquired pneumonia in patients with COPD using inhaled corticosteroids was strongly associated with old age, obesity, DM, smoking, and a long course of the illness. These may be considered as additional risk factors for CAP among ICS using subgroup.

Keywords; Community-acquired pneumonia, CAP, Chronic obstructive pulmonary disease, COPD, Corticosteroids, ICS

BACKGROUND

According to the World Health Organization, COPD is the third leading cause of death globally. Chronic obstructive pulmonary disease (COPD) is responsible for 6% deaths per annum and its mortality distribution remains almost same in all income groups[1]. This illness claims the lives of almost 2.5 million individuals each year. The leading cause of COPD risk is cigarette smoking. Additional important risk factors include occupational dust exposure and hereditary alpha-1 antitrypsin deficiency.[2] Breathing difficulties, a persistent cough that may or may not be productive, and decreased activity tolerance are common symptoms of COPD. These symptoms often worsen while the illness is exacerbated.[3] Use of long-acting β_2 agonists (LABA) in treating COPD in conjunction with ICS is a norm nowadays. Recent clinical trials have shown the efficacy of ICS with LABA in improving lung health and function and reducing the frequency of acute exacerbations (AE) and mortality. However, long-term ICS use has shown an increase in the risk of CAP in COPD patients.[4]

Data published so far shows that the risk of CAP varies with the type of ICS and dose of ICS [5]. It has been observed that pneumonia in patients with COPD has poor outcomes in terms of severity, hospitalization, and complications when compared with patients without COPD.[6] COPD often co-exists with other diseases like bronchiectasis, CVD, chronic kidney disease,

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dyslipidemia, diabetes, hypertension, and lung cancer and may have a significant impact on overall prognosis [7]. A systemic review done in Spain by Miravitlles M *et al*[8] revealed that COPD patients receiving corticosteroids have 41% higher chances of developing pneumonia.

This research assisted in determining the prevalence of CAP among COPD patients receiving ICS in our local population, as we lacked such study in our local population. It gave baseline information regarding our population and identified the problem's current magnitude. Moreover, recent data supports that inhaled ICS-related pneumonia is less severe in lethality; our study would provide grounds for further research once a positive relationship between these two variables was established. And it would help clinicians to anticipate CAP and manage it timely to decrease disease morbidity and mortality. So, we aimed to determine the association between community-acquired pneumonia (CAP) with inhaled corticosteroids among patients with chronic obstructive pulmonary disease (COPD).

MATERIAL AND METHODS

From the 15th of October 2020 to the 14th of April 2022 (18 months), a cross-sectional study was carried out in the medical and pulmonology department of the Nishtar Hospital in Multan. The institutional review board granted ethical permission on 02-10-2020 vide order 12351. Each individual provided written informed consent before being included in the research.

A total of 300 patients of either gender, between the ages of 30-70 years, diagnosed with COPD with no history of hospitalization in the previous 30 days, disease duration (COPD) for more than six months, taking corticosteroids for six months were enrolled in the study by using a non-probability consecutive sampling technique. Subjects having congenital heart disease, ischemic heart disease, cardiomyopathy, bronchial asthma, bronchiectasis or restrictive lung disease, or occupational exposure to asbestos, silica, or coal based on history were ruled out from the study. COPD was labeled in those with either FEV1/FVC <70% and <15% reversibility of FEV1 after β2-agonist use done six months back or with already established diagnosis based on history and medical records along with taking inhaled corticosteroid therapy as prescribed by the clinician for more than six months. CAP was diagnosed if the patient had a fever ≥101˚F, cough, difficulty breathing, and tachypnea (24 breaths/minute) for more than three days, along with radiological findings such as air space opacity, lobar consolidation, or interstitial opacities. Patients smoking at least ten cigarettes per day for more than two years were labeled as smokers.

The patient's biodata and demographic information were recorded using a pre-designed questionnaire. Age, gender, residence status, socioeconomic position, diabetes, hypertension, obesity, dyslipidemia, smoking history, and length of disease were among the demographics gathered and recorded. Once registered, all patients underwent clinical examination and chest x–rays to diagnose pneumonia.

Data were analyzed using SPSS v.24. For patient age and disease duration, the mean and standard deviation were determined. Frequencies, along with percentages, were recorded for gender, obesity, dyslipidemia, residential status, monthly family income, age groups, and the presence of pneumonia, smoking, diabetes, and hypertension. Chi-square analysis was used to establish an association between CAP and ICS-treated COPD patients. Stratification was done to overcome effect modifiers such as age, gender, smoking, diabetes, obesity, hypertension, disease duration, and residential status. After stratification, the Chi-Square test was applied again. P value $\leq$ 0.05 was considered significant.

RESULTS

A total of 300 COPD patients who met the inclusion criteria were enrolled. Of 300 cases, 190 (63.3 %) were males, while 110 (36.7%) were females. Our study's patients had an average age of 56.63 ±3.4 years. According to the findings of our study, 198(66%) patients were older than 55. Out of 300, 155 (51.7%) belonged to the urban population while 145 (48.3%) lived in rural areas. Regarding socioeconomic status, 188 (62.7%) belonged to poor socioeconomic status, while 112 (37.3%) patients were in the middle-income group. Diabetes was present in 123 (41%), and 117 (39%) were hypertensive. The mean BMI was 25.43 ± 4.15 kg/m^{2,} and 22.0 % of cases were obese. The mean duration of illness was 18.39 ± 7.76 months, and 204 (68.0%) had more than one year of illness. Of these 300 study cases, 200 (66.3%) were smokers, while dyslipidemia was noted in 136 (45.3%) (Table-I).

The total number of COPD patients who were on Inhaled corticosteroids (ICS) was 247 (82.3%), while the patients who developed community-acquired pneumonia were 43 (14.3%). Out of 43, two patients who were not on ICS developed CAP. On chi-square analysis, there was a significant association between ICS and CAP ($p<0.05$) (Table-II)

The frequency of CAP was stratified against gender, age groups, residential status, diabetes, hypertension, obesity, COPD duration, and smoking. CAP had a significant association (p-value ≤ 0.05) with the old age group (>55 years), urban population, diabetes, smoking, and COPD duration of more than 12 months as shown in Table-III.

Table-I: Demographic properties of study population (n=300).

Variables		Frequency	Percentage
Gender	Male	190	**63.3%**
	Females	110	**36.7%**
Residence	Rural	145	**48.3%**
	Urban	155	**51.7%**
Dyslipidemia	Yes	136	**45.3%**
Age Groups	≤55 years	102	**34%**
	>55 years	198	**66%**
Diabetics	Yes	123	**41%**
Hypertensive	Yes	117	**39%**
Smoking	Yes	200	**66.7%**
Socioeconomic	Poor	188	**62.7%**
Status	Average	112	**37.3%**
Obese	Yes	66	**22%**

Table-II: Association between ICS and CAP.

		CAP		Total	
		Yes	No		
ICS USE	No	2	51	53	P- value= **0.016** (<0.05)
	Yes	41	206	247	
Total		43	257	300	

Table-III: Stratification of various factors with CAP in patients using ICS.

VARIABLES		ICS USE		Community-Acquired Pneumonia		Total	P-Value
	GROUPS			Yes	No		
Gender	MALES N=190	ICS	No	2	37	37	0.087
			Yes	25	138	153	
	FEMALES N=110	ICS	No	0	16	16	0.074
			Yes	16	78	94	
Age Group	≤55 years (N=102)	ICS	No	2	10	12	0.853
			Yes	17	73	90	
	>55 years (N=198)	ICS	No	0	41	41	**0.08**
			Yes	24	133	157	
Residence	Rural (N=145)	ICS	No	2	19	21	0.27
			Yes	24	100	124	
	Urban (N=155)	ICS	No	0	32	32	**0.026**
			Yes	17	106	123	
Diabetes	Diabetics (N=123)	ICS	No	2	17	19	**0.022**
			Yes	39	65	104	
	Non-Diabetics	ICS	No	1	33	34	0.625

	(N=177)		Yes	1	142	143	
Hypertension	Hypertensive (N=198)	ICS	No	2	9	11	0.438
			Yes	31	75	106	
	Non-HTN (N=198)	ICS	No	0	42	42	0.076
			Yes	10	131	141	
Obesity	Obese (N=66)	ICS	No	1	27	28	**0.0001**
			Yes	17	21	38	
	Non-Obese (N=234)	ICS	No	1	24	25	0.252
			Yes	24	185	209	
Smoking	Smokers (N=200)	ICS	No	0	31	31	**0.019**
			Yes	26	143	169	
	Non-Smokers (N=100)	ICS	No	2	20	22	0.263
			Yes	15	63	78	
Disease Duration	≤12 Months (N=96)	ICS	No	2	15	17	0.416
			Yes	16	63	79	
	>12 months (N=204)	ICS	No	0	36	36	**0.013**
			Yes	25	143	168	

DISCUSSION

Chronic obstructive pulmonary disease is a common ailment that may be prevented and managed according to the global strategy for treating, managing, and preventing it.[9] It may be identified by a persistent airflow limitation that is often progressive and associated with an aggravated chronic inflammatory reaction to hazardous particles or gases in the lungs or airways. It is proved in multiple clinical trials, that a fixed-dose combination of an ICS and long-acting β_2-agonist (LABA) used in the treatment of COPD, not only decreases the frequency of COPD exacerbations[10] by about 25% but also slows down disease progression[11] and prognosis of disease also improves.[12] Use of this combined therapy not only has better bronchodilator properties but is even better at preventing exacerbation when compared to bronchodilator therapy alone.[13.] Variations in results in terms of exacerbation frequency and prognosis have been noted with various ICSs.

However, it has been identified that ICS use in COPD is a potential risk factor for various adverse effects including a higher risk of pneumonia, tuberculosis, atypical mycobacterial infections, bone fracture resulting from osteoporosis, poor diabetic control, and local effects like oral thrush, hoarseness of voice, cough. Rabe KF *et al*[14] have recorded higher CAP frequency among COPD patients using ICS. The chances of CAP were more likely with lipophilic potent ICSs such as fluticasone and less likely with beclomethasone and budesonide.[15]

In our study, we had 190 (63.3%) male patients, and 110 (36.7%) female patients. Most studies[16,17,18] also show male preponderance but a study from Peshawar revealed otherwise.[19] Hence it is important to study more local data to generate population-based evidence.

Our study population had an average age of 56.63 ±3.4 years. Our study showed that 198 patients, or 58.7%, were older than 55. Studies conducted by Jamil M[18] and Iftikhar *et al*[20] also reported a higher frequency of COPD among patients above 50 years.

Of the 300 study cases, 145 (48.3%) were from rural areas, whereas 155 (51.7%) belonged to metropolitan areas. One hundred eighty-eight people (62.7%) had low socioeconomic levels, while 112 (37.3%) had a modest income. In 123 (41 percent) of the research participants, diabetes was present. 117 (39 percent) of the study patients had hypertension. The average BMI of the research participants was 25.43 ± 4.15 kg/m2, and 66 (22.0 percent) of them were obese. Research by Mahishale *et al*[21] also found a diabetes prevalence of 21.24% among COPD patients, which is slightly less than our study's findings. It may be due to higher prevalence of diabetes in our population.

The average disease duration was 18.39 ± 7.76 months, and 204 (68.0%) had more than one year of illness. 200 (66.6%) of the 300 research participants had a smoking history, and 136 (136%) had dyslipidemia (45.3 percent). According to research by Ahmad *et al*[18] and Iftikhar *et al*[21] from Peshawar, 37.5% and 38% of participants had ever smoked respectively, which is inconsistent with the findings of our investigation. It may be due to other factors for COPD like bidi chewing and naswar use.

Community-acquired pneumonia was noted in 43 (14.3%) patients. According to Lin *et al*[22] study, which was carried out in Taiwan, 19.5% of cases of CAP in COPD patients occurred with ICS use, which is consistent with our study's findings. Ritchie A *et al*.[23] conducted a population-based case-control study in the UK and found that ICS use was associated with 26% increased risks of CAP in COPD patients. They also observed that recent ICS use was more strongly related to CAP.

Lin SH *et al*[24] has identified high prevalence of CAP among elderly age group and diabetics. Our results are congruent with these findings. However, Lin SH *et al*. didn't establish this association of advanced age and diabetes with CAP in ICS using subgroup but we studied it in ICS using subgroup and established association of these two variables with CAP in ICS subgroup which is a peculiar feature of our study. Mkorombindo T *et al*[25] noticed that CAP was more frequent in those ICS patients who had low BMI and advanced age. Our results are partially consistent with these findings because we also found high prevalence of CAP in ICS subgroups with advanced age but we found that it was more common among obese patients. This discrepancy may again be attributed to high prevalence of diabetes among obese patients.

CONCLUSION

Patients with the chronic obstructive pulmonary disease had a significant frequency of community-acquired pneumonia, according to our research. Significant association have been shown between community-acquired pneumonia and ICS use in the older age group (>55 years), urban population, diabetics, smokers, and COPD duration of more than 12 months. All medical professionals caring for such individuals should consider them at risk for developing community-acquired pneumonia. Early detection and treatment of community-acquired pneumonia may enhance clinical outcomes and lower disease-related morbidity.

LIMITATION OF STUDY

As the study was conducted only in a tertiary care center so it may not give a true picture of disease prevalence. Moreover, the frequency of CAP was not determined separately in different types of ICS so we can't tell with surety which type of ICS and what dose of ICS is notorious for causing CAP. Further studies may be required to address other aspects of ICS-related CAP among COPD patients which have not been covered in our study. Additional work is required to identify risk factors for increased incidence of CAP in ICS using subgroup.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

AUTHOR CONTRIBUTION

Shahzad Alam Khan: Conception or design of the work, literature search, questionnaire design, data collection

Faisal Ramzan: Literature search, Data analysis, data interpretation, drafting

Nasir Jamal Khan: Data collection and drafting, literature search

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CASE REPORT

CO-INFECTION OF INFLUENZA AND DENGUE VIRUSES IN A PATIENT WITH GRAM-NEGATIVE BACTEREMIA- A CASE REPORT

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ABSTRACT

Co-infection with influenza and dengue virus is a rare occurrence, and when combined with gram-negative bacterial infection, can present a complex clinical picture. We present the case of a 68 years old male, with prostrate carcinoma and prior trans-urethral resection of the prostate 1-year ago, now presented with symptoms of profuse sweating and undocumented fever for 4 days. He was positive for both Influenza A and Dengue virus and developed Gram-negative bacteremia. The patient manifested pyrexia, chills, severe body aches, and laboratory investigations revealed thrombocytopenia and hemolytic anemia. Patient was managed with supportive care, intravenous antibiotics, and supplemental oxygen. After 2 weeks of hospital stay, patient was discharged. Early recognition and initiation of appropriate therapy can lead to a favorable outcome in such cases. Thus, co-infection with influenza, dengue, and gram-negative bacteria can present with a complex clinical picture and requires prompt diagnosis and management.

Keywords: Co-infection, Dengue virus, Hypoxia, Influenza, Thrombocytopenia.

BACKGROUND

Dengue fever is a common vector-transmitted disease in tropical regions. The vector in this disease is the mosquito *Aedes aegypti*. This constitutes a major burden on the health system with 400 million cases reported worldwide annually.[1] Dengue virus bears 04 serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. Clinically it presents as a minor viral infection in most patients.[2] Symptoms may include fever, malaise, rash, muscle and joint pains, severe headache, vomiting, nausea and lymphadenitis, lasting for 2-10 days.[3] The more severe manifestations of dengue hemorrhagic fever may be seen in about 1 out of 20 patients infected with the dengue virus. Caution signs are: abdominal pain, vomiting, fatigue, polypnoea, bleeding from orifices, agitation and altered mental status.[4] Patients with warning signs require hospital admission and close monitoring. Treatment for dengue infection is mainly supportive as it is a self-limiting disease bearing mortality rate >1%. With treatment, mortality associated with it ranges from 2-5%; however, if left untreated, mortality may be as high as 50%.[5]

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The virus detection was accomplished by Polymerase chain reaction (PCR), viral cultures, and non-structural protein or serologically through Enzyme-linked immunosorbent assay (ELISA) for IgM and IgG antibodies. The IgM are detectable after 1 week of infection until 3 months, while IgG may be detectable from day 7 for up to 3 years.[6]

Influenza is another common viral infection and is among the leading causes of mortality across the globe. Seasonal influenza results in 3-5 million infections and 250,000-500,000 annual mortality.[7] Its incubation period is 2 days on average. Treatment includes neuraminidase inhibitors (oseltamivir, zanamivir). Oseltamivir is effective in treatment of influenza A and B viruses if administered within 48 hours of the onset and duration of treatment is 5 days.[8] However, treatment should be instigated irrespective of the duration of symptoms in severe disease, hospitalized and immunocompromised patients. Annual influenza vaccine is recommended in dependent of the susceptibility status to prevent infection. Thus, a case of co-infection of dengue and influenza virus is presented below.

CASE REPORT

A 68 years old male, diagnosed case of prostate carcinoma with a previous history of trans-urethral resection of the prostate 1 year ago presented with symptoms of profuse sweating and undocumented fever for 4 days. At the time of presentation, he had a heart rate of 118 beats/min, blood pressure of 114/60 mm of Hg, a temperature of 36^{o}C and oxygen

saturation of 98% at room air. His random blood sugar was 283 mg/dl. Abdominal examination revealed mild tenderness in Right hypochondrium and a chest examination showed diminished right-sided breath sounds. The rest of the examination was unremarkable.

The hemoglobin of patient was 7.4 g/dl, platelets of 63000 /Ul, total leucocyte count of 6400/Ul, creatinine of 1.24 mg/dl and lactate of 44.1 mg/dl. Liver function tests showed Alanine transaminase (ALT) 38 U/L (Ref range: 4-36 U/L), aspartate aminotransferase (AST) 30 U/L (8-33 U/L), gamma-glutamyl transferase (GGT) 72 U/L (5-40 U/L), bilirubin 1.17 mg/dl (<1 mg/dl), albumin 2.49 g/dl (3.4-5.4 g/dl). Further workup showed Malaria Parasite smear and COVID-19 (PCR) negative while Dengue IgM and Influenza A were positive. He was negative for Dengue NS1 antigen. He was started on oral oseltamivir 75mg twice daily for 5 days and was managed symptomatically for dengue fever.

His blood cultures showed growth of *Escherichia coli* sensitive to amikacin, chloramphenicol, ciprofloxacin, co-trimoxazole, and ertapenem. tetracycline, gentamicin, imipenem, levofloxacin, meropenem, piperacillin- tazobactam, tobramycin. Ultrasound abdomen revealed mild bilateral hydronephrosis. The patient was given piperacillin-tazobactam initially which was later switched to meropenem due to persistent fever spikes. His Hb dropped to 6.6 on day 4 of hospitalization, without any overt bleeding. The patient was transfused 1 packed red blood cell.

During the transfusion, his oxygen requirements gradually increased from room air to 2 liters to 10 liters/minute of supplemental Oxygen. The patient had distended neck veins and bilateral basal crepitations. Chest X-ray showed bilateral confluent perihilar infiltration suggestive of pulmonary edema. This was attributed to transfusion-related acute lung injury (TRALI) and underlying infections. He was managed in the intensive care unit with diuretics and non-invasive ventilation with 10 liters/minute of supplemental Oxygen for 2 days after which he was stepped down to high-dependency unit monitoring. His platelets over the subsequent week dropped to a nadir of 30 000 /Ul with no evidence of overt bleeding.

His clinical course remained static over the next few days with persistent fever spikes and minimal hypoxia requiring 2 liters/minute of supplemental oxygen. COVID-19 PCR was repeated twice and was negative. Computed Tomography chest, abdomen and pelvis (done on day 15 of admission) showed bilateral lung airspace changes with septal thickening. Bilateral moderate-volume pleural effusions were seen along with associated atelectasis.

Over the next few days, he reported lower backache for which Magnetic resonance imaging lumbosacral spine was performed that showed osteomyelitis and a 2.3 x 1.1 cm fluid collection in region of L5 to S1 in epidural space. CT guided drainage of fluid; aspirate cultures revealed growth of *Escherichia coli* (sensitive to amikacin, chloramphenicol, ciprofloxacin, cotrimoxazole, ertapenem, gentamicin, imipenem, levofloxacin, meropenem, piperacillin/tazobactam. Histopathology revealed vague necrotizing granulomas. Initial studies including Ziehl-Neelsen stain and MTB Gene Xpert were negative. Acid-fast bacilli cultures were reported negative at 6 weeks of incubation.

Over the next few days, the patient remained afebrile and his platelet counts improved to 86,000 /ul. He was discharged on intravenous ertapenem for 2 weeks due to single daily dosing with follow-up in the Infectious disease clinic with repeat imaging post-discharge. Repeat imaging was done after 4 weeks of antibiotics. Repeat MRI lumbar spine showed near complete resolution of abscesses. Currently, the patient is off antibiotics for more than 2 months and doing well.

DISCUSSION

Co-infection of dengue and influenza virus is an unusual occurrence with limited reports in literature. We report a case of Dengue Virus and Influenza A co-infection with *Escherichia coli* bacteremia and multiple spinal abscesses. A case series from Brazil included 4 patients with fatal dengue and influenza co-infection. Histopathological and necropsy findings revealed peripheral cyanosis, bilateral pleural effusion, pericardial effusion, heart enlargement, hepatomegaly and congested kidneys. Microscopy showed cerebral edema, congestive heart and edema, hypertrophy of myocardial fibers and dilation of the chambers. Lung hyaline membranes were thick and had interstitial pneumonitis and intra-alveolar edema. Kidneys had acute tubular necrosis and liver showed cholestasis. A study found four patients with fatal influenza A (H1N1) pdm09 and dengue virus coinfections, similar to our case report. Clinical, necropsy, and histopathologic findings in all cases were indicative of influenza-dengue coinfections, and all cases, including

ours, had laboratory confirmation of both infections. Four cases of laboratory-confirmed coinfection of deadly influenza A(H1N1) pdm09 with DENV occurred during the dengue and influenza season in 2012 and 2013 in Ceará. The study concluded that the influenza and dengue seasons coincide in Ceará, which led to diagnostic difficulties [9]. The lung fragments were positive for Influenza A (H1N1) virus by real-time RT-PCR, and liver fragments were positive for dengue viruses (DENV) by immune histochemistry. Our patient however has no evidence of heart failure or liver involvement. One case report from India of a 27-year-old male who presented with fever, headache, myalgia, dry cough and runny nose tested positive for dengue NS1 and IgM. Another corroborating study conducted on a 27-year-old male presented with fever, headache, myalgia, dry cough, running nose, sore throat, and increasing breathlessness with his vital signs showed low blood pressure, rapid pulse, and decreased oxygen saturation was reported. Laboratory investigations revealed low platelet count and elevated hematocrit. Dengue virus infection was confirmed through positive NS1 and IgM dengue ELISA tests, as well as positive real-time polymerase chain reaction (RT PCR) for dengue serotype DEN1. Chest X-ray showed left pleural effusion, and subsequent evaluation identified H1N1 pneumonia. With supportive management and oseltamavir his condition gradually improved and he was discharged after 20 days.[10]

Animal models have demonstrated high DNV titers in spleen, lungs and liver tissue that increase risk of pneumonia by impairing monocyte function in dengue and influenza co-infection.[11-12] Poor outcomes associated with influenza and dengue virus co-infection in a pregnant woman presented with fever, headache and myalgia, were reported.[13] Her initial workup showed thrombocytopenia and proteinuria and she was managed along the lines of pre-eclampsia. Later, her dengue IgM was positive. Chest X-ray showed bilateral pleural effusion. The patient was shifted to ICU and later died. Post-autopsy lung tissue showed microangiopathic changes similar to that seen in dengue, while lung tissue staining and PCR revealed influenza infection.[11-12] Our patient was shifted to ICU. However, early diagnosis and prompt treatment resulted in early improvement and step down from the ICU, and later discharge from the hospital. Our findings were supported by a report that thrombocytopenia was found in both dengue and gram-negative sepsis.[14] A peripheral blood smear provided the evidence of hemolytic anemia by showing characteristic findings such as schistocytes (fragmented red blood cells), spherocytes (spherical-shaped RBCs), polychromasia (increased reticulocytes), increased unconjugated bilirubin, and anisocytosis/poikilocytosis (variation in size and shape of RBCs). These findings, along with clinical symptoms and other laboratory parameters, can aid in the diagnosis of hemolytic anemia. However, in the presence of hemolytic anemia and fragmented erythrocytes, the diagnosis of thrombotic thrombocytopenic purpura should be considered, because it is rare but life-threatening condition presented as a complication of both influenza and dengue infection.[15]

CONCLUSION

In conclusion, co-infection with influenza, dengue, and gram-negative bacteria can present a complex clinical picture and requires prompt diagnosis and management. Early recognition and initiation of appropriate therapy can lead to a favorable outcome.

CONFLICT OF INTEREST

There is no conflict of interest to declare by any authors.

AUTHOR CONTRIBUTION

Rabia Islam Abbasi: Manuscript writing, Literature search, concept

Salma Muhammad Abbas: Literature search, proofread and finalization of report

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CASE REPORT

A RARE CASE OF BILATERAL SPONTANEOUS TENSION PNEUMOTHORAX IN A PATIENT WITH MUCORMYCOSIS

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ABSTRACT

Mucormycosis is an invasive fungal infection seen in immunocompromised hosts. Here a rare case of mucormycosis with pulmonary involvement followed by bilateral spontaneous tension pneumothorax is described. Bilateral spontaneous tension pneumothorax is a rare and fatal condition. We present a case of 3 years old child, diagnosed case of acute Leukemia. During the course of induction chemotherapy, he was hospitalized with fever and diarrhea. He was being managed on lines of neutropenic colitis. During the hospital stay, the child developed sudden respiratory distress and seizures. Chest X-ray showed bilateral spontaneous tension pneumothorax. Immediate bilateral chest tubes insertions were done. He was also electively intubated. After successful lung expansion, the trial of weaning off the ventilator was given and patient was successfully extubated. CT Thorax after lung re-expansion showed few pneumatoceles with no bronchopleural fistulous communication. CT Brain and para nasal sinuses showed fungal rhinosinusitis with intracranial extension. Nasal endoscopy and debridement of necrotic tissue was done. Tissue cultures showed the growth of mucor species. The patient was also started on amphotericin B that was later changed to Posaconazole. He responded well to anti-fungal treatment and there was no recurrence of pneumothorax.

Keywords: Mucormycosis, Tension pneumothorax, Bronchopulmonary fistula

BACKGROUND

Mucormycosis represents a group of fungal infections that can involve any organ. The fungus is found in soiled matter. Most commonly, the organs involved are the skin, paranasal sinuses, orbits, brain, lungs, and gastrointestinal tract.[1] Mucormycosis is known to cause life-threatening infections in immunosuppressed individuals like those with diabetes mellitus, hematologic malignancy, and solid organ or stem cell transplant recipients. Pulmonary mucormycosis is a rapidly progressive and devastating infection.[2] Early recognition is important to avoid complications. We present an unfortunate case of a child with pulmonary mucormycosis who developed bilateral spontaneous tension pneumothorax and became hypoxic. The patient was intubated, and chest drains were passed. Later, the growth of mucor was seen in nasal aspirate cultures. The patient was successfully treated with antifungals.

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CASE REPORT

A 3-year-old male child of Asian ethnicity, diagnosed having Pre – B acute lymphoblastic leukemia, was started on induction chemotherapy. On 23rd day of chemotherapy, he was admitted with fever, loose stools and few pustular lesions on lips. His complete blood count showed an absolute neutrophil count of 0. He was started intravenous piperacillin/tazobactam. After 4 days, his counts started recovering and the fever settled. He developed a seizure like activity on 5th day of admission that was followed by tachycardia and respiratory distress. His oxygen saturations dropped, and the ICU team decided to take him to ICU. Before shifting to ICU, his saturation dropped to 68 %, code blue was announced, and emergency intubation was done. Arterial blood gas showed respiratory acidosis with PH of 7.02 pre intubation. Chest X ray on arrival at ICU showed bilateral tension pneumothorax with a cavitary lesion in left lung (Figure-I). Immediate chest drains insertions were done on both sides.

His CT chest was done to see the underlying cause of the pneumothorax. CT chest revealed scattered cavitary lesions with ground glass haze which were suggestive of fungal infection, a reverse halo sign was present (Figure 2 a and b). However, based on radiological findings suspicion of pulmonary mucormycosis was high.

Child was started on empirical oral anti-fungal treatment with voriconazole, but he continued to spike

fever. Beta D Glucan was positive with value of 277 pg/mL (≥ 80 is positive) suggestive of fungal infection. His CT paranasal sinuses and CT brain were done to look involvement of infectious process. CT para nasal sinuses findings were compatible with fungal rhinosinusitis. CT brain showed an enhancing lesion in anterior cranial fossa that was suggestive of intracranial extension of the process. CSF studies came out to be normal. Voriconazole was switched to intra venous amphotericin B to broadly cover mold infection as there was cerebral extension of the infective process. ENT consultation was sought, and he underwent functional endoscopic sinus surgery. Necrotic tissue was removed and sent for histopathology along with bacterial and fungal cultures. Right sided maxillary enterostomy and ethmoidectomy was done. Histopathology of necrotic tissue showed necro-infalmmatory debris consistent with fungal infection. Ulcerated respiratory mucosa in background. Cultures of the specimen showed growth of mucor species (Figure-III). The patient responded well to treatment, became afebrile after 7 days.

His Chest X ray also showed good lung expansion, followed by removal of chest drains. The child was treated as a case of disseminated mucormycosis with rhino-cerebral and pulmonary involvement. He received 1.5 months of intravenous amphotericin B, and later switched to oral Posaconazole. CT chest showed good resolution of cavitary lesions after 5 months of treatment (Figure-IV). However, CT Para nasal sinuses showed resolution of changes after 3 months (Figure-V). Minimal mucosal thickening was noted in the paranasal sinuses. Child was continued on oral Posaconazole, and his chemotherapy was re-started with good tolerance. The child was planned to be kept on posaconazole till the end of his chemotherapy and until cancer comes in remission.

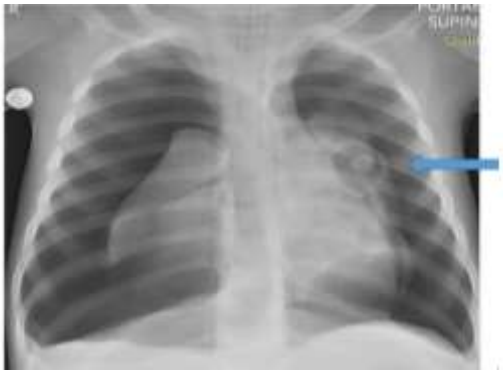
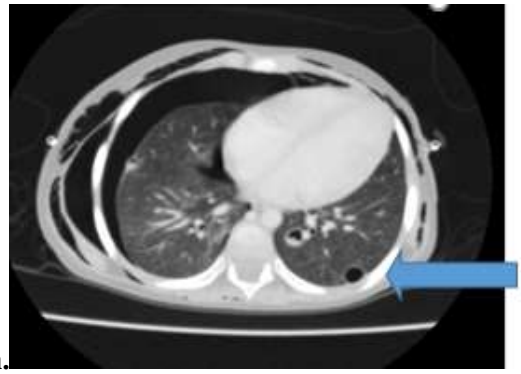


Figure-I: Chest X-ray showing bilateral pneumothorax and cavitary lesion with soft tissue density (arrow)



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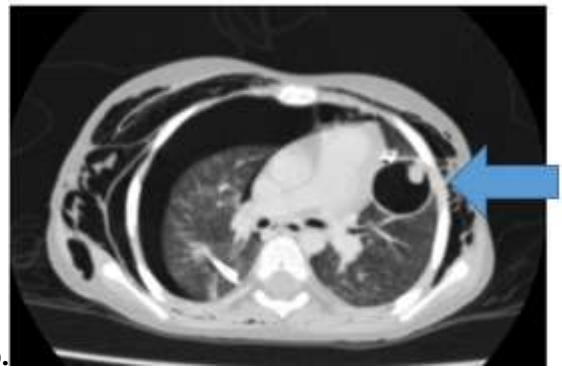

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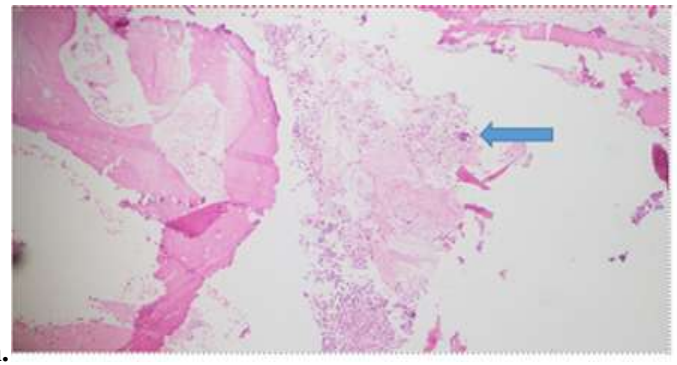
Figure-II: (a and b): CT Chest showing extensive pneumomediastinum and bilateral emphysema, persistent pneumothorax, scattered cavitary lesions with soft tissue density (arrows)



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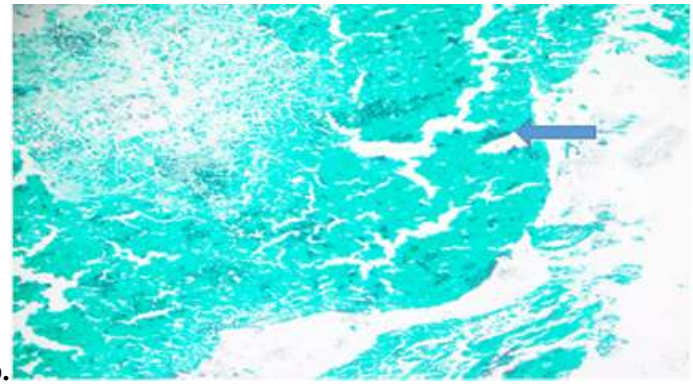

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Figure-III: a) Histopathology of nasal mucosa biopsy showing growth of mucor (arrow), b) Grocott's methenamine silver stain showing growth of mucor (arrow).

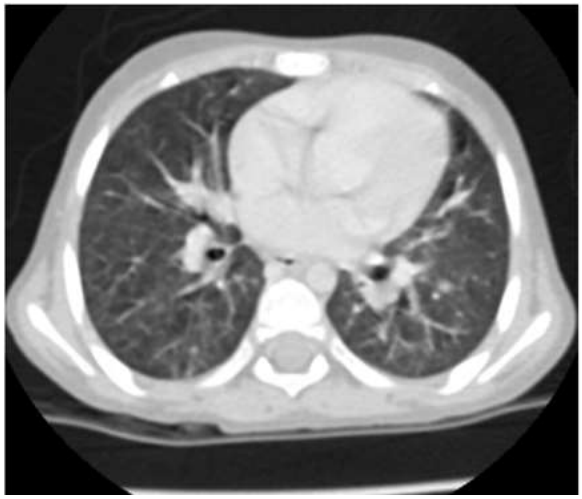

Figure-IV: CT Chest showing good resolution of cavitary lesions.

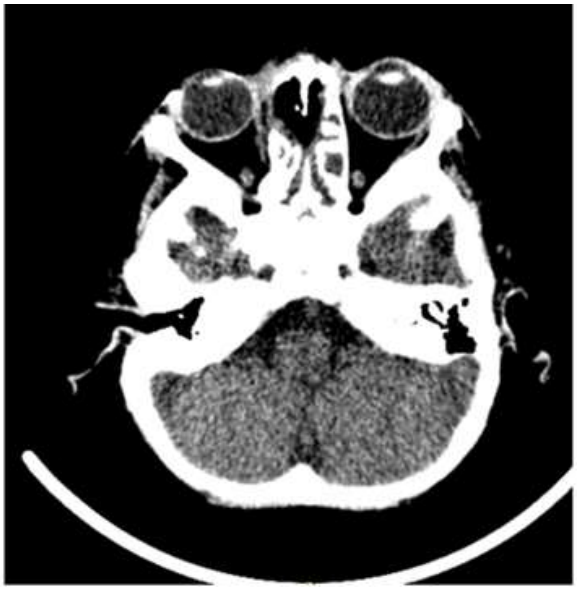

Figure-V: CT para nasal sinuses showing redemonstration of erosive changes in the cribriform plate along with changes of right maxillary enterostomy and ethmoidectomy. Minimal mucosal thickening noted in the paranasal sinuses.

DISCUSSION

The occurrence of pneumothorax in mucormycosis is rare with limited case reports in literature. We report a case of bilateral spontaneous tension pneumothorax due to disseminated mucormycosis, in a child who was immunosuppressed due to active chemotherapy. A case report from New Zealand, stated a patient with diabetes, end-stage renal disease, and sarcoidosis who was on steroids developed large hydropneumothorax due to mucormycosis. CT Chest showed nodular lesions. Bronchoscopy and BAL was negative for any organism. CT guided biopsy revealed growth of mucor.[3] He was successfully treated with amphotericin B, Posaconazole and drainage therapy like in our case. Another case reported from Cincinnati, Ohio included a 48-years old diabetic lady who presented with fever and chest pain. She became hypoxic and developed tension pneumothorax; CT chest showed a classical reverse halo sign. A chest tube was passed and the patient was treated with antibiotics for necrotising pneumonia. She further deteriorated, was intubated and passed away. Lung specimen biopsy on autopsy specimen showed mucor growth. This case highlights the importance of radiological diagnosis of mucormycosis by presence of reverse halo sign.4 Like in our case, bronchoscopy and BAL cultures were negative but presence of reverse halo sign was diagnostic of mucor alongwith growth of mucor in nasal biopsy specimen. A case report from India included a diabetic, alcoholic male who developed hydropneumothorax secondary to mucormycosis. CT chest later on confirmed presence of bronchopleural fistula due to mucor. The patient underwent pneumonectomy and Gomori methenamine silver stain showed aseptate hyphae that was suggestive of mucormycosis. This patient needed surgical management for broncho pleural fistula developed due to mucor.[5] A case of spontaneous pneumothorax by mucormycosis is also reported from USA that occurred in a patient who was COVID-19 positive. The patient underwent pigtail catheter insertion followed by treatment by amphotericin B. Pleural fluid cultures showed growth of mucor –Rhizopus species. Later-on, he was discharged on maintenance dose of Posaconazole.[6] A case report from Iran stated a patient of glomerulonephritis who was on immunosupressive therapy, he developed orbital edema and facial puffiness. During hospital stay he developed pneumothorax and was ventilated due to respiratory distress. Due to immunosuppressed state, he was treated for Pneumocystis jervocii pneumonia and only fluconazole was added for oral thrush. Later on, CT chest showed characteristic reverse halo sign and scattered pulmonary nodules with ground glass haze [7]. He was started on amphotericin B but unfortunately the patient could not survive. Tongue biopsy later showed growth of mucor. This case, like our case, had rhino-orbital mucormycosis alongwith pulmonary mucormycosis. This highlights the importance of early treatment of mucormycosis with presence of reverse halo sign and high clinical suspicion.

Mucormycosis represents fungal infections caused by genus Mucorales and can involve different organs including brain, paranasal sinuses, skin, lungs and gastrointestinal tract. Pulmonary mucormycosis represents 25 % of the cases of mucormycosis with mortality rates reaching up to>50%.[1] It is uncommon in healthy individuals and is seen in immunosuppressed population including those with uncontrolled diabetes, hematological malignancies, chronic renal failure, on immunosuppressive therapy and organ transplant recipients.[4] Pulmonary mucormycosis may have nonspecific symptoms such as fever, cough, chest pain or hemoptysis due to invasion of vasculature. It may have a subacute presentation with extensive subcutaneous emphysema or spontaneous pneumothorax as in our case.[8\] It is easily misdiagnosed due to non-specificity of symptoms. Radiological appearance of pulmonary mucormycosis may vary like its clinical manifestations ranging from consolidation, nodules and cavities.[9]

It remains challenging to diagnose pulmonary mucormycosis. Histopathology on tissue cultures remains the gold standard for diagnosis. As cultures obtained on bronchoalveolar lavage can be negative. Mucormycosis species appears as non-septate hyphae with right angle branching on histopathology.[10\] Tissue sampling may be time consuming and may delay diagnosis. Thus, imaging plays a significant role in diagnosis. CT features may vary from consolidations, pulmonary nodules to Reverse Halo sign. Reverse halo sign is thought to be specific for mucormycosis, which is described as a consolidation with a central ground glass haze.[11] Pneumothorax is a rare finding of mucormycosis. Whenever pneumothorax is suspected due to mucormycosis, further diagnostic imaging and pathology should be done to confirm diagnosis of invasive fungal infection, as delaying it results in increased mortality.[7] Our patient had characteristic cavitary lesions, reverse halo sign on his CT chest, that led to our suspicion of pulmonary mucormycosis along with rhino-cerebral mucormycosis.

Once the diagnosis of mucormycosis is established, treatment should be started without further delays (<6 days). Amphotericin B, a polyene antifungal, is the choice of drug for mucormycosis. However, drug susceptibility is different for different mucor species. Drug concentration in the lungs is lower than in other tissues. Hence, higher doses are needed to treat pulmonary mucormycosis with amounts reaching >10mg /kg. Liposomal amphotericin B is the preferred preparation.[12] Due to necrosis associated with this infection, drug penetration is also compromised. For this reason, surgical debridement is done along with antifungal therapy. Studies have shown better outcomes when surgical treatment is combined with medical therapy. Unless surgery is contraindicated or there are patient dependent risk factors, surgical debridement is advised to combine with antifungal therapy.[13]

For patients who do not tolerate amphotericin B or are not improving despite being on optimal therapy, a triazole fungicide Posaconazole has shown good outcomes. Posaconazole can be used as salvage or maintenance therapy. It can be used in patients who need long term therapy.[14] Isavuconazole is a new triazole, that has shown good antifungal activity against mucormycosis. However, Voriconazole is not shown to be useful in treating mucormycosis. Some studies have suggested use of liposomal amphotericin B in combination with echinocandins (Caspofungin), however there is no data available to use two antifungals as first line therapy.[15]

The duration of treatment varies according to patient related factors. Ideally, it should be continued until complete clinical and radiological recovery has occurred, also there is good control of immunosuppressed state.[14,15]

CONCLUSION

Pulmonary mucormycosis is a rare condition but has high mortality. Whenever it is suspected, physicians should do appropriate investigations promptly to avoid unnecessary treatment with voriconazole. Early diagnosis of mucormycosis is challenging and delayed due to non-specific manifestations. Histopathology is time-consuming. Delaying diagnosis and treatment has high mortality rates. Presence of spontaneous pneumothorax in addition to reverse halo sign and increased nodularity with ground glassing should raise suspicion of mucormycosis specially in immunocompromised population. Once diagnosis is established, appropriate anti-fungal therapy should be started immediately, also surgical options wherever applicable should be used as an adjunct to improve outcomes and reduce mortality in patients with mucormysosis.

CONFLICT OF INTEREST

There is no conflict of interest to declare by any authors.

AUTHOR CONTRIBUTION

Mahreen Sana: Literature search, study design, data analysis, drafting

Maha Anwar: Literature search, data collection, concept, drafting

Faheem Mahmood Butt: Data collection, literature search, concept

Adnan Amir: Literature search, analysis, concept

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You CH. Lee KY, Chey WY, Manguy R. Electro gastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterol 1980; 79: 311-314. Chapter in a book: Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. WB Saunders, Philadelphia 1974; 457-472.

- et al. is written after 6 authors names, list first 6 authors' names then write et al. in references.
- Write complete surname and convert first name and middle name to the initials, following each surname. e.g., Rimondini LR, Zolfanelli B, Bernardi F, Bez C.

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.

PLAGIARISM

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