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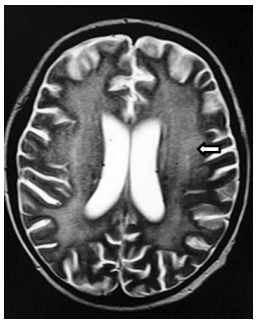

Axial T2- weighted MRI of brain

Courtesy: Dr Ejaz A. Khan, Shifa International Hospital, Islamabad.

Injections in Pakistan: Are we safe?

In Pakistan about 80% of the population gets treatment from the private practitioners' clinics. These clinics mostly consist of single room structure where consultation, injection administration, dressing of wounds, stitching and other types of minor procedures are done[1]. Studies from different parts of Pakistan have indicated unsafe and overuse of injection practices among Health Care Workers (HCW) especially working at clinics[2]. A study in two districts of Karachi reported that on average 13 injections are being received per person per year which is the highest injections rate throughout the world[2]. Majority of these injections (almost 75%) are administered with contaminated (reused) syringe[3]. Likewise, multi-dose vials are used at most clinics in Pakistan, substantiating the transmission risk of blood borne infections not only among HCWs but also among patients visiting these facilities[2]. There is no culture of sharp bins availability in these outpatient settings. Contaminated syringes, needles and other medical waste are disposed off along with other wastes in community garbage-bins, which on one hand expose scavenger children and workers of municipal corporation at risk of acquiring sharp injuries (SI) and blood borne infections; and on the other hand provide opportunity to illegal dealers to recycle these contaminated syringes and needles for reuse-increasing the transmission probability of blood borne pathogens (BBP)[3].

The incidence of needle stick injuries (NSI) among HCWs in developing countries is far higher than in their developed counterparts. Our study among private practitioners in slum area of Karachi Pakistan, reported 26.7% prevalence of NSI during last one year. Another study among HCWs from both public and private first level care facilities found annual rate of NSI to be 1.9/HCW/Year[4]. The rate of NSI was significantly higher among HCWs from public facilities than private clinics. Another study from first level care facilities in rural Sindh, reported 50% prevalence of NSIs among HCWs[5]. According to WHO, 40-65% of hepatitis B & C viruses infections among HCWs in the developing world are attributed to occupational NSI[6]. Since the prevalence of hepatitis B and C virus infections among general population is high in Pakistan[7], coupled with relatively higher burden of NSIs and inadequate hepatitis B vaccination among HCWs from first level care facilities[8] therefore occupational risk of acquiring blood borne infections is also higher in Pakistan.

In addition, majority of HCWs working at first level care facilities in Pakistan are unregulated; lack essential qualification, awareness of universal/standard precautions, and knowledge regarding modes of transmission of BBPs[4]. Therefore, it is the responsibility of government, medical, nursing, paramedical and non governmental organizations and other stake holders to develop and implement occupational safety programs at outpatient facilities such as mandatory hepatitis B vaccination, cost effective availability of essential safety equipments, surveillance of sharp injuries and post exposure prophylaxis & treatment. Furthermore, health care regulations are needed to ban reuse of ordinary disposal syringe, and unsafe disposal of sharps. Combine efforts should be initiated to promote use of auto-disable syringes and mandatory availability of sharp bin in each facility by subsidizing the cost. If proper measures were not taken timely, the burden of blood borne infections among HCWs at outpatient settings will very soon enter in an epidemic.

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Prolonged Febrile Neutropenia: Risk factors and Outcome in Pediatric Oncology Patients

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Abstract

Background
Febrile neutropenia (FN) is a common and potentially life-threatening complication of childhood cancer where children are at increased risk for severe, recurrent or new bacterial and fungal infection. Early initiation of empirical antibacterial may lead to substantial improvement in morbidity and mortality. This study describes the demographic, clinical and laboratory features, risk factors and outcomes of prolonged FN (PFN) in pediatric cancer patients.

Methods
This was a retrospective chart review (2011-2012) of paediatric cancer patients (age 1month to 15 years) with discharge diagnosis of FN at Aga Khan University. PFN was defined as FN persisting beyond 5 days. Data was collected for demographic, laboratory findings and outcome (ICU admission and mortality) data. Results are presented as mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Data was stratified into two group, patients with only FN and patients with PFN to identify the risk factors associated with the development of PFN in pediatric oncology patients. A p-value of < 0.05 was considered statistically significant.

Results
We analyzed 872 hospitalizations of pediatric cancer patients with FN. The mean age of the study population was 5±4 years. Majority of them were males (n=559,64%). ALL (68%) was the most common diagnosis followed by AML (12%), lymphoma (10%) and sarcomas (6%). Cause of neutropenia was identified in only 58 (43%) patients. The common causes were URTI (22%), BSI (7%), pneumonia (4%), infectious diarrheas (2%) and UTI (1%). Age less than 5 year (p= 0.043), AML (p=0.019), patients who received chemotherapy within 2 week of FN (p=0.007), severe neutropenia ANC < 50 (p < 0.041), platelets count < 50,000/mm^3 (p < 0.027), fungal infection (p <0.001), and pneumonia were identified as risk factors associated with development of PFN (> 5 days) in pediatric cancer patients. A total of 25 (2.9%) patients required PICU admission and overall 12 (1.4%) patients expired. Both PICU admission (OR 5.4) and mortality (OR 8.1) were statistically significant in patients with PFN versus FN.

Conclusions
Younger age, AML, severe myelosuppression, fungal infection and pneumonia were identifiable risk factors associated with development prolonged FN. PICU admission and mortality were higher in patients who had PFN.

Key Words
Febrile neutropenia, prolonged, pediatric, oncology, mortality fungal infection

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Introduction

Febrile neutropenia (FN) is a common and potentially life-threatening complication of childhood cancer where children are at increased risk for severe, recurrent or new bacterial and fungal infection especially when FN persists.[1]

Over the last few decades, there have been major advances in the treatment and outcomes of childhood cancer that have largely been achieved by aggressive treatment including systemic antineoplastic and radiation therapy that have secondary effects on a variety of normal cells including hematopoietic elements of the bone marrow.[1] Chemotherapy induced neutropenia is a common complication in children who receive chemotherapy and renders them extremely vulnerable to life threatening infections. Epidemiological studies have demonstrated a high incidence of sepsis in paediatrics cancer patients receiving chemotherapy. It was seen in approximately 12.8% and 17.4% children aged 1-9 years and 10–19 years respectively, making FN a worrying and serious complication in childhood cancer treatment.[1,2]

In recent years, several studies from developed countries have evaluated the risk factors for bacteremia or poor outcomes among patients with cancer and helped to establish the current guidelines for the treatment of FN.[3-5] However, despite major advances in the understanding and presence of recommendations for the treatment of FN, it renders children extremely vulnerable to life threatening infections and continues to be a significant cause of morbidity and mortality in pediatric patients with cancer.[1,6,7]

Mortality associated with FN in cancer patients ranges from 2–6% in children.[8,9] Initiation of empirical antibacterial

depending on the local microbial susceptibility data in a febrile neutropenic child, is the single most important intervention leading to improved childhood survival. Before this approach was instituted in the early 1970s, mortality rate from gram negative infections, approached 80%, but with the widespread use of effective empirical antibiotics, the overall mortality rate has significantly declined. [6-9] Considering that the overall mortality rate for FN episodes was 10% a decade ago, the current 2–4% rate indicates that advances in management have had a positive impact. Currently the Infectious Diseases Society of America has published general guidelines for use of antimicrobial agents in neutropenic patients with unexplained fever.[11]

Many studies from developed countries have been reported regarding the importance and management of FN. However, reports from developing countries are lacking and scarce reports are available from Pakistan. We intend to describe the burden of FN , it's demographic, clinical and laboratory data in paediatric cancer patients at a tertiary care hospital in Karachi. We also aim to determine the risk factors and management outcomes of prolonged FN in these patients.

Material and Methods

We conducted a retrospective chart review of all pediatric (age 1month to 15 years) oncology patients admitted with FN in the pediatric oncology unit, at Aga Khan University Hospital (AKUH) in Karachi, Pakistan over a period of 2 years from January 2011 to December 2012.

Fever was defined as a single oral temperature of >38.3ºC or a temperature of >38.0ºC sustained over a 1-h period or on more than one occasion in a 24-hour period.[12] Neutropenia was defined as an absolute neutrophil count (ANC) of less than 0.5x109/l (<500/mm3).[12] If the FN persisted beyond 5 days then it was labelled as prolonged FN (PFN). For those patients who had more than one admission for FN, each admission was counted as separate case. Data was collected on demographic features, type of malignancy, phase of chemotherapy, clinical features at presentation, duration of symptoms, presentation location (Emergency department, clinic, or inpatient ward), initial laboratory findings including total white blood cell (WBC) count, ANC, platelet count; microbiological data, antibiotic(s) used, radiological finding (if applicable) and data on outcomes, whether needed PICU admission or not and discharge disposition (dead or alive). All patients were treated as inpatients following the international pediatric fever and neutropenia guideline.[13]

The data was analyzed by using SPSS version 20.0 (IBM, Chicago, USA). Summary statistics were used to describe the cohort. Results are presented as mean and standard deviation for continuous variables and frequency and percentages for categorical variables. Data was stratified in two group, patients with only FN and patients with PFN to identify the risk factors associated with the development of PFN in pediatric oncology patients. A p-value of < 0.05 was considered statistically significant. The study was approved by the Ethical Review Board (ERB) of Aga Khan University, Karachi.

Results

The total number of admissions in the pediatric oncology unit during the study period were 2,516 with FN being identified in 872 (35%) patients. Out of 872 febrile neutropenic patients, 737 (85%) had FN of less than 5 days versus 135 (15%) patients with prolonged FN (FN > 5 days). FN and PFN admission rate among all pediatric oncology patients were 35% and 5% respectively.

Demographic features, clinical characteristics of the patients and their hospitalizations are presented in Table 1. The mean age of the study population was 5.3 years (± SD 4.1). Majority of them were males (n=559, 64%), with male: female ratio 1:1.8. Most of them were admitted through the emergency department (n=719, 82%). Almost two thirds (n=590; (68%) of FN children had acute lymphoblastic leukemia (ALL) followed by acute myeloid leukemia (n=105; 12%), lymphoma (n=86; 10%) and sarcomas (n=51; 6%). Pyrexia alone (n=715, 82%) was the commonest presenting complaint followed by poor oral intake (69%), vomiting (19%), cough (16%), mucositis (14%), diarrhea, urinary complaints and rash.

Cause of FN was identified in only 58 (43%) patients, commonest being URTI (n=192; 22%), blood stream infections (BSI) (n=58; 7%), pneumonia (n=31; 4%), infectious diarrheas (n=16; 2%) and urinary tract infections (UTI) (n=11; 1%).

Analysis was performed for the identification of risk factors for development of PFN (Table 2). Age less than 5 years (OR=1.5; p= 0.043), AML (OR=1.8; p=0.019), patients who received chemotherapy in the preceding 2 weeks of the FN episode (OR=1.9; p=0.007), severe neutropenia ANC < 50 (OR=1.5; $p < 0.041$), platelets count < 50,000/mm^3 (OR= 1.5; $p < 0.027$), fungal infection (OR=15.6 ; $p < 0.001$), and pneumonia were found as risk factors associated with development of PFN in pediatric cancer patients.

A total of 25 (2.9%) patients required PICU admission and overall 12 (1.4%) patients expired. Both PICU admission (OR:5.4) and mortality rate (OR: 8.1) were significantly associated with PFN.

Discussion

A number of studies from developed countries have evaluated the risk factors for bacteremia or poor outcomes and there has been an increasing interest in stratifying patients with FN into risk categories to establish the current guidelines for the treatment of FN.[8,12,14-15] The current study used a single institution experience from a developing country to identify the risk factors and outcomes for development of PFN in pediatric cancer patients.

Table 1: Baseline characteristics, haematological data and outcomes of the study patients (N=872)

Characteristics		Number	Percentage (%)
Gender	Male	559	(64.1%)
	Female	313	(35.9%)
Age	< 5 year	506	(58.1%)
	> 5year	366	(41.9%)
Cancer Types	ALL	590	(67.7%)
	AML	105	(12.2%)
	Lymphoma	86	(9.9%)
	Sarcomas	51	(5.8%)
	CNS tumors	11	(1.3%)
	Others	28	(3.2%)
Presentation location	Emergency Department	719	(82.4%)
Received Chemotherapy within the preceding 2 weeks		656	(75.2%)
Absolute Neutrophil Count	250-500	254	(29.1%)
	50-250	279	(31.9%)
	<50	339	(38.9%)
Hemoglobin	< 9 gm/dl	538	(61.7%)
Platelet count	50-150 x 10^3 mm^3	508	(58.3%)
	<50 x 10^3 mm^3	364	(41.7%)
Inotropic Support required		37	(4.2%)
PICU Admission		25	(2.9%)
Died		12	(1.4%)

Table 2: Risk factors and outcome for prolonged febrile neutropenia (n = 872)

Variables*		FN (< 5 days) n = 737	PFN (> 5 days) n = 135	Odd Ratio	p-value
Gender	Male	464	95	1.4	0.099
Age	< 5 year	417	89	1.5	0.043
Cancer Type	AML	81	24	1.8	0.019
Received Chemotherapy within the preceding 2 weeks		542	114	1.9	0.007
ANC	< 50	276	63	1.5	0.041
Platelet count	<50 x 10^3/mm^3	296	68	1.5	0.027
Hemoglobin	< 9 gm/dl	445	93	1.4	0.061
Bacterial Infection		36	12	1.9	0.060
Fungal Infection		5	13	15.6	<0.001
Pneumonia		14	9	3.7	0.004
Outcome Variables					
PICU Admission		13	12	5.4	<0.001
Expired		5	7	8.1	<0.001

AML, Acute Myeloid Leukemia; ANC, Absolute Neutrophil Count.
*For each variable of risk factor, not having the specific risk was used as the reference group.

In many studies, age group is reported as a significant independent risk factor for both longer length of stay and death.[8] Although infancy has been cited as a high-risk pediatric age group, most studies have very few infants and young children to evaluate this relationship.[16-19] In the current study, the risk of PFN was highest in young children (57% vs. 66%; OR 1.5; p=0.043). This may be due to differences in the primary cancer type and type of chemotherapy received by the two age groups. One of the criteria established in the management of FN is the absolute neutrophil count at presentation, with ANC counts < 0.2 x10^9/L being associated with a high risk of infection and bacterial sepsis.[20] Recently, the value of the absolute monocyte count has been shown to correlate highly with the duration and outcome of febrile neutropenic episodes.[16,21,22] Our data showed that severe myelosuppression indicated by severe neutropenia and severe thrombocytopenia were associated with the prolongation of febrile neutropenic episodes. This is consistent with studies in pediatric febrile neutropenic patients that have identified that patients with severe neutropenia and thrombocytopenia are at highest risk for adverse events.[8,23] This relationship serves as an important prognostic factor in the management of febrile neutropenic episodes.

For the evaluation of risk by cancer type, ALL was used as the reference category. It should be noted that an odds ratio of less than 1 for any of the cancer types in this analysis indicates a lower risk of the outcome as compared to ALL; it does not denote a protective effect as there were no non cancer controls. In comparison to ALL, a diagnosis of AML was associated with two-fold increased risk of PFN and adverse outcome. Earlier studies report a three-fold longer length of stay as well as higher death in patients with AML as compared to ALL.[8] A diagnosis of lymphoma and osteosarcoma/Ewing sarcoma or rhabdomyosarcoma was associated with a significant reduction in risk of composite adverse outcome. This is consistent with studies in adult populations that have identified solid tumors as having a lower risk of adverse outcomes.[4] Similarly, pediatric studies have identified patients with leukemia or relapse of leukemia as being at high risk for bacterial infections.[9,24]

Additionally, invasive infections (i.e., sepsis, bacteremia, pneumonia and fungal infection) were significantly associated with the prolongation of FN in our study. A diagnosis of sepsis or bacteremia conferred a 1.9-fold increase in the risk (5% vs. 9%), although the p value (p=0.06) was not significant. This is because of early recognition, prompt initiation of antibiotic. However, despite the widespread use and availability of powerful antibiotics, bacteremia/ sepsis remains the most important independent prognostic marker for poor outcome and/or mortality. Pneumonia was associated with an increased risk of PFN and poor outcomes in our study, similar to other studies that showed a three to eight-fold increase in the risk of PFN and death respectively.[8] Fungal infections were associated with an increased risk of PFN similar to other pervious published reports.[8]

A recently published study [25] reported similar composite adverse outcomes in febrile neutropenic pediatric cancer patients. In our series, <3% patients required PICU admission with <2% mortality. Both outcome variables were significantly associated with PFN. However, the mortality rate in some pediatric studies of FN has ranged from 0.7% to 3.9%.[9,16,21,22]

Conclusion

Our study indicates that patients with younger age, diagnosis of AML, severe neutropenia (ANC < 50), severe thrombocytopenia (platelets < 50,000/mm^3), fungal infection and pneumonia should be considered at high risk for the development of prolonged FN. Children with PFN were eight times more likely to die compared to FN. Prospective studies of PFN among children enrolled in larger studies my confirm these risk factors further.

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ORIGINAL ARTICLE

Knowledge of Tuberculosis Patients Regarding their Disease and its Treatment

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Abstract

Background
There is little research in developing countries to guide policy change, based on assessment of behavior of patients. Tuberculosis is a serious public health problem and there is dearth of data on patient's behavior and understanding of disease in our community. The present study was designed with the objective of assessing the knowledge of adult patients with tuberculosis regarding their disease and its treatment.

Methods
This was a cross sectional study, carried out in both outpatients and inpatients of pulmonary and extra pulmonary tuberculosis, who were on anti-tuberculosis treatment at Combined Military Hospital Sialkot from January 2013 – January 2014. The patients having recurrence or relapse of tuberculosis were excluded. A specially designed questionnaire was filled for each patient. The analysis of questions was done using Microsoft excel and frequencies are reported.

Results
A total of 230 (164 males and 66 females) responders with age range12-88 years were studied. Majority (n=123), were matriculate and knew the name of the disease they were suffering from. Directly Observed Treatment (DOT) was adopted in only 61(26%) cases and 74 (44%) out of remaining 169 patients taking medicine themselves, admitted occasional or frequent missing of dose. Adverse effects were reported by 109 (47%) patients and 33 patients discontinued medication due to side effects. Majority (n=198; 86%) understood that their disease is transmissible to others but only 100 (51%) were adopting measures to avoid transmission to others.

Conclusion
The understanding of the disease and its treatment is sub optimal in our patients and only one third have access to DOTs regimen.

Key Words
Directly Observed Treatment (DOT), Treatment knowledge. tuberculosis

Introduction

Tuberculosis is an important and serious public health problem, particularly in developing countries. It affects about one third of the worlds' population.[1] As per World Health Organization (WHO), largest numbers of new cases are seen in South East Asia. The treatment of active tuberculosis remains the only effective strategy for stopping the spread of the disease as a diseased person may infect up to 15 people every year if not treated properly.[2] Complete and continuous treatment is absolutely necessary for effective tuberculosis control programs.[3] Many factors may affect adherence to treatment for tuberculosis like socioeconomic factors, age, gender, occupation and behavioral factors.[4-8] Understanding of the disease itself, factors that affect transmission, importance of compliance to treatment are important for the patients to comprehend for adequate treatment.[9] This study was carried out to determine the knowledge of adult patients with tuberculosis regarding their disease and its treatment.

Materials and Methods

The study was carried out from January 2013 to January 2014 at Combined Military Hospital, Sialkot, which is a 700 bedded tertiary care hospital. Patients with diagnosis of either pulmonary or extra pulmonary tuberculosis and on anti-tuberculosis treatment were included in the study, whereas patients having relapse or recurrent disease were excluded. A predesigned proforma was filled for each patient. The proforma collected information on educational status, knowledge of disease, duration of illness and treatment, number of tablets/injections used and mode of taking medicine (self/DOT), compliance to medications, undesirable effects of treatment, knowledge of the causative agent, disease transmission and adoption of measures to stop transmission and finally any educational classes regarding disease. A total of 230 patients were interviewed. Analysis was done using Microsoft excel and frequencies and percentages are reported.

Results

During the study period 230 patients were recruited for the analysis, 164 were male and 66 females. Age range was 12 to 88 years. The educational status of the patient was matriculate (n=123), under-matric (n=40) and 55 were uneducated. Only 12 patients were graduates. A total of 223 patients had the knowledge that they were suffering from tuberculosis, whereas 7 patients had no knowledge of their disease. Majority (60%) of the patients, had the disease for the last 6 months to one year, while 92 patients had disease for one year or more. Analysis of knowledge of treatment and adherence to treatment is given

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in table-I and table II. Majority, (n=198; 86%) patients had the knowledge that their disease can be transmitted to others but only 100 (51%) had the knowledge how to avoid transmission and were adopting it.

Table I: Knowledge of treatment and compliance to antituberculous thearpy by study subjects (n=230)

Variables	Response n (%)
Duration of treatment	
< 3 months	38 (16.5)
3-6 months	82 (35.7)
6-12 months	90 (39.1)
> 01 year	20 (8.7)
Mode of taking medicine	
Self	169 (73.4)
DOTs	61 (26.6)
Missing of dose in self administered patients	
Never missed	95 (56.2)
Occasionally missed	60 (35.5)
Frequently missed	14 (8.3)
Feeling of undesirable effects	
Never felt	121 (52.6)
Occasionally felt	69 (30.0)
Frequently felt	40 (17.4)
Ever stopped the treatment	
Yes	33 (14.3)
No	197 (85.7)

Table II: Knowledge of disease and disease transmission, by the patients on anti tuberculous treatment (n=230)

Parameters	Analysis n (%)
Knowledge of causative agent (n=230)	
Bacterial	122 (53.0)
Viral	20 (8.7)
Fungal	33 (14.3)
Do Not Know	55 (24.0)
Knowledge of disease transmission to others (n=230)	
Yes	198 (86.0)
No	32 (14.0)
Having Knowledge of transmission & Practice to stop transmission (n=198)	
Know and adopt measures	100 (50.5)
Know but do not adopt measures	27 (13.6)
Do not know measures	71 (35.9)
No knowledge of transmissibility	32 (13.9)

Discussion

Knowledge regarding tuberculosis and its treatment is suboptimal in our population and only one third of the subjects receive DOT therapy. Most of the subjects are treated without the DOTs regimen and there is questionable compliance either due to poor knowledge or occurrence of side effects.

The knowledge regarding treatment of tuberculosis, treatment adherence and transmission of the infection is very important for patients suffering from tuberculosis. Interruption and incomplete treatment are major hurdles in the treatment and control of this disease.[2] Improper treatment is also a major cause of drug resistance which is becoming a major public health threat for TB care and control.[10]

In most studies of assessment of knowledge of TB, males are predominant and the same was observed in our study.[2] This could be either due to the predominance of disease in males or due to differential health seeking behavior. Majority of the patients in the present study were at least matriculate, whereas in some other studies from developing countries educational status was comparatively lesser.[2,11] As per WHO, Directly Observed Treatment (DOT) is an important strategy for tuberculosis control,[12] but unfortunately a very small proportion of patients receive DOT therapy. Variable results of treatment adherence have been reported in national and international studies.[2,13] In our study almost one third of the subjects reported stopping treatment during the course of therapy. Quite a number of patients did not know the cause of their disease as was observed in a study at Karachi and abroad.[2, 14, 15] In the present series although majority of the patients knew that their disease can be transmitted to others like in a study at Iraq,[16] but patients either did not know preventive techniques or were not adopting the measures to avoid transmission. Similar results were found from other studies from Sudan and Karachi.[11, 14] Almost all of the patients admitted said that there were no educational classes, methods, messages for the awareness of their disease and all of them agreed that such classes / counseling sessions should be made available and can be very beneficial. In a study from South Africa training of nursing staff and health care personnel for this purpose was found very effective.[17]

Conclusions

DOTs for treatment adherence was adopted by only one third of the patients and its implementation can lead to improved compliance. Patient centered intervention and educational measures to improve the knowledge of disease transmission can be useful strategy for TB control.

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Cefotaxime alone versus Cefotaxime and Clarithromycin Combination Therapy for the Treatment of Community Acquired Pneumonia in Children 2 Months -12 Years of Age at POF Hospital.

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Abstract

Background
Treatment of community acquired pneumonia with a combination of beta lactam and macrolide has shown promising outcomes in adults. The combination therapy is not widely studied in children. Therefore the present study aims to compare the efficacy of Cefotaxime alone with Cefotaxime and Clarithromycin for treatment of community acquired pneumonia (CAP) in children.

Methods
A retrospective analysis of 384 clinical records of children (2 months- 12 years) admitted to the department of pediatrics with diagnosis of CAP was done. Only cases which received Cefotaxime alone or in combination with Clarithromycin having uncomplicated pneumonia were included. Children with chronic illnesses predisposing to pneumonia, severe malnutrition, need for intensive care and bronchial asthma were excluded. The outcome variables were length of hospital stay, duration of fever and supplemental oxygen.

Results
Out of 348 cases included in the study, 72% received Cefotaxime alone and 28% in combination with Clarithromycin. Children who received combination therapy were of older age ($p<0.02$), had fever> 100^0 F ($p<0.01$) and had received antibiotics prior to admission ($p<0.04$). Length of hospital stay and duration of fever were significantly shorter in the group with combination therapy ($p <0.04$).

Conclusion
Combination therapy with Cefotaxime and Clarithromycin was associated with shorter length of hospital stay and fever duration and this regimen should be tested in larger studies to be recommended for use in children.

Key words
pneumonia, pediatric, macrolides, community

Introduction

Community acquired pneumonia (CAP) is one of most common childhood infectious disease in developing countries.[1] The estimated annual incidence of CAP is 151 million new cases worldwide. Severe pneumonia requiring hospital admission is seen in 7-13% of these cases. Community acquired pneumonia is also responsible for approximately 2 million pediatric deaths.[2] Streptococcus pneumoniae is considered as the most common cause of CAP.[2] Recently, an increase in the incidence of pneumonia caused by atypical organisms, mycoplasma pneumoniae and clostridium pneumoniae is also seen in Pakistan and India.[3,4] The improved vaccination rate for Hib conjugate vaccine (Hemophilus influenza type b vaccine) and addition of pneumococcal vaccine to the EPI vaccination schedule in Pakistan may be partly responsible for this trend.

Guidelines for management of community-acquired pneumonia recommend empiric therapy with a macrolide and beta-lactam when infection with mycoplasma pneumoniae is a significant consideration. However it is uncommon to identify specific causative agent of pneumonia in clinical settings.[5,6] The uncertainty regarding the exact causative organism and its antimicrobial sensitivity leads to empiric use of broad spectrum antibiotics like third generation cephalosporins in combination with macrolides in cases hospitalized for severe pneumonia.[7] Treatment of bacterial pneumonia in adults with combination of macrolide and beta lactam antibiotic has shown to reduce mortality.[8, 9] The effectiveness of such a combination therapy in children is not clear. We studied the efficacy of combination regimen including a beta lactam (cefotaxime) and a macrolide antibiotic (clarithromycin) compared to cefotaxime alone, on clinical outcomes in the treatment of children hospitalized with community-acquired pneumonia (CAP).

Materials and Methods

This retrospective cohort study was conducted at the department of Pediatrics, POF Hospital, Wah Cantt. We reviewed the medical records of children between 2 months and 12 years, admitted from 1st April 2013- 31 March 2014 with a diagnosis of pneumonia. Out of these case records only those meeting the following operational definition of CAP were selected: History of cough and/ or breathing difficulty, rapid breathing (WHO tachypnea thresholds for diagnosing pneumonia[10]), abnormal white cell count (<5000/µl or >15000/µl), fever (axillary temperature) > 100^0F within first 24 hours of admission and /or radiological evidence of pneumonia (infiltrates or consolidation).

We further scrutinized the records to narrow down the study

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cohort to only those cases which received either cefotaxime alone or in combination with clarithromycin in the first 48 hours after admission.

Co-existing chronic conditions predisposing to recurrent pneumonia, previous diagnosis of asthma, hospital acquired pneumonia, complicated pneumonia (empyema, effusion or pneumothorax), and transfer to intensive care within first 24 hours of admission and incomplete clinical records were considered as exclusion criteria.

Outcome variables included length of hospital stay measured in hours, duration of fever in hours and duration of supplemental oxygen in hours. Fever was defined as axillary temperature >100° F. Duration of fever was calculated as duration in hours from the time of admission to time of last recorded reading of temperature. Duration of supplemental oxygen was calculated from time of admission to time of discontinuation of oxygen therapy.

Percentages of categorical variables (patient characteristics) were calculated. Two sample t-test was applied to compare the percentages in the two study groups. P-value < 0.05 was considered significant. Mean values for outcome variables were determined. A preliminary Levene test for equality of variance in the mean values from two study groups indicated that the variances of two groups were significantly different. As a result two sample student t-test assuming unequal variance was used to calculate p values. P-value < 0.05 was considered significant. Statistical analysis was done using SPSS version 10.0

Results

During the study period a total of 507 children with a diagnosis of pneumonia were admitted in the Department of Pediatrics POF Hospital, Wah Cantt. Only 386 (76.13%) case records fulfilled the eligibility criteria (Figure 1). Final study cohort comprised of 348 clinical records out of which 28% (n=95) received cefotaxime and clarithromycin combination therapy with in first 24 hours of admission and remaining 72% (n=253) received cefotaxime alone. Later, 9.8 %(n=38) of records fulfilling eligibility criteria initially were excluded after detailed reviewing. Out of these 21(n=55.2%) had incomplete daily progress records, 12 patients (31.5%) got transferred to other hospitals and 5 patients (13.1%) left against medical advice.

It was noted that 33.6% patients in combination therapy group and 23.3% patients in the monotherapy group were between 5 to 12 years of age (p<0.03). In addition history of antibiotic use before admission was seen in 31.5% of patients in combination therapy group and in 21.3% of monotherapy group (p< .04). Fever > 100°F was seen in 69.4% of patients in combination therapy group while only 44.6% patients had such finding in mono therapy group (p<0.01) (Table 1).

The analysis of records for outcome variables showed that the

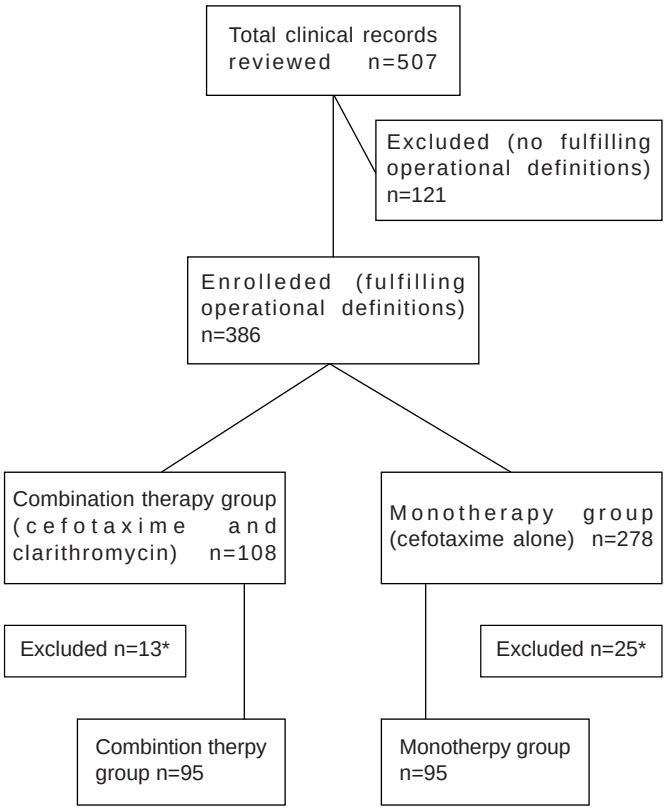

Fig 1. Flow chart of the study

*21 had incomplete daily progress records, 12 patients got transferred to other hospitals and 5 patients left against medical advice.

mean length of hospital stay was 24 hours shorter in the combination therapy group, (p<0.04). Same was true for mean duration of fever which was 6 hours less in the combination therapy group (p<0.04). However there was no significant difference in the mean duration of supplemental oxygen requirement (p<0.18) (Table 2).

Discussion

CAP remains one of most common causes of pediatric mortality in Pakistan in spite of advent of effective antibiotics and universal vaccination against Hemophilusinfluenzea and Streptococcus pneumoniea.[10] Cases of severe pneumonia usually require hospitalization. The decision to treat with antibiotics is often challenging. Initial antibiotic therapy is empiric and the exact pathogens are not commonly known at the time of diagnosis.[11] Several organizations have published guidelines for treatment of childhood CAP and unanimously recommend use of antibiotics in such cases.[9, 12, 13] Antimicrobial prescribing practices vary widely from hospital to hospital. The empiric antibiotics are chosen based upon patient's age, clinical presentation and knowledge of common causative organisms in a particular community. Beta lactam antibiotics are recommended as first line treatment for community acquired pneumonia. In addition British Thoracic Society recommends that macrolide antibiotic may be added if first line antibiotic

Table 1: Clinical and demographic characteristics of children admitted with pneumonia (n=348)

	Total patients n=348 (%)	Combination therapy group, n=95(%)	Mono therapy group, n=253(%)	p-value
Age 2 months-3yrs.	195(56)	44(46.3)	151(59.6)	0.02
Age >3 yrs.- <5 yrs.	62(17.8)	19(20)	43(16.9)	0.68
Age5 year-12 years	91 (26.1)	32 (33.6)	59 (23.3)	0.03
Male	190 (54.5)	54 (56.8)	136 (53.7)	0.72
Fever> 100^0 F	179 (51.4)	66 (69.4)	113 (44.6)	0.01
Abnormal WBC count	127 (36.4)	43 (45.2)	84 (33.2)	0.62
Antibiotics use before admission	84 (24.2)	30 (31.5)	54 (21.3)	0.04
Positive x-ray findings	108 (31.1)	33 (34.8)	75 (29.6)	0.07
Convulsion	10 (2.0)	2 (2.1)	8 (3.1)	0.28
Inability to drink	4 (1.1)	1 (1.0)	3 (1.1)	0.32
Wheeze	14 (3.6)	3 (3.1)	11 (4.3)	0.62
Stridor	10 (2.8)	2 (2.1)	8 (3.1)	0.13
Altered conscious level	6 (1.8)	2 (1.1)	4 (1.5)	0.38

Table 2: Comparison of the outcome variables between the children who received mono therapy versus combination therapy

Outcome Variable	Combination therapy group, n=95	Mono therapy group, n=253	p-value
Mean length of hospital stay hours (+ SD)	72 (+ 6.23)	96 (+ 4.02)	0.04
Mean duration of supplemental oxygen. hours (+ SD)	15 (+2.56)	21 (+2.02)	0.18
Mean duration of fever hours (+ SD)	43 (+2.48)	52 (+3.76)	0.04

(Two sample t-test assuming unequal variance in two groups was used to calculate p-values)

gives no response or if Mycoplasma pneumoniea infection is suspected or in cases of very severe pneumonia.[12]

According to Pediatric Infectious Diseases Society and Infectious Diseases Society of America guidelines empiric combination therapy with a macrolide (oral or parenteral) in addition to beta lactam antibiotic should be prescribed for the hospitalized children in whom M. pneumoniea or C. pneumoniea are a significant consideration.[13]

In the present study we compared beta lactam (cefotaxime) monotherapy with beta lactam and macrolide (cefotaxime and clarithromycin) combination therapy. We found significantly decreased length of hospital stay and decreased duration of fever in those who received combination therapy. Previous studies comparing these two treatment modalities found either no significant difference in length of hospital stay with combination therapy or such benefit only in older school age children.[14] We observed shorter length of hospital stay in < 3 years of age children as well as in older 3-12 years age group. In the combination therapy group, older children with severe pneumonia were predominant and perhaps macrolide combination therapy resulted in earlier response and shorter duration of admission. In the past researchers did not study additional variables like duration of fever and supplemental oxygen.[14, 15] However we included these outcome variables in

the present study and shorter duration of fever with combination therapy was a new finding observed in the study cohort. On the other hand duration of supplemental oxygen was not significantly different in the two groups. The study of variables reflecting clinical response to treatment like fever and supplemental oxygen duration was something which was an addition to existing research. Past studies have compared rates of readmission into treatment groups, however, we did not analyze this variable in present cohort because of non-availability of follow up data. Leyenaar *et al* compared ceftriaxone monotherapy and ceftriaxone plus macrolide combination therapy retrospectively and found that cost of combination therapy was higher as compared to monotherapy.[16] Although cost of treatment was not analyzed in the present study but shorter hospital stay may compensate for increased cost of combination treatment. Martinez *et al* demonstrated lower mortality in cases of pneumococcal pneumonia treated with a combination of macrolide and beta lactam antibiotic in adults.[17] Mortality rate was not analyzed as primary outcome variable and case records of patients requiring intensive care or complicated pneumonia were excluded at the outset.

The present study has some limitations. Cost analysis could not be done. Secondly rate of readmission to hospital couldn't be determined as follow-up data was not available. Only admitted cases with mostly severe form of community acquired pneumonia were included. The high frequency of antibiotic use before admission in combination therapy group can't be ignored.

In the era of universal pneumococcal and Hemophilusinfluenzea vaccination in Pakistan, it is important to study the comparative effects of different therapeutic regimens for pneumonia which may be caused by atypical organisms or mycoplasma like pathogens requiring addition of a macrolide to treatment.

Conclusion

This retrospective study showed that cefotaxime and clarithromycin combination therapy for community acquired pneumonia in children 2 months to 12 years of age resulted in shorter duration of fever and hospital stay compared to monotherapy with cefotaxime alone. The duration of supplemental oxygen was similar between the two study groups.

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ORIGINAL ARTICLE

Inhibitory Activity of Colicin Producing *Escherichia coli* Isolated from Clinical Specimens

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Abstract

Colicins are protein toxins produced by *Escherichia coli* against other *E. coli* or closely related species.

Objective
To detect colicin producing *E. coli* and its inhibitory activity against *E. coli* and other bacteria.

Methods
One hundred *E. coli* strains obtained from urine, stools, vaginal swabs, pus; wound swabs and twenty, *E. coli* from different food samples were collected. Twenty strains of *Pseudomonas* spp. and *Enterobacter* spp. were also collected from other clinical samples. Bacterial strains were inoculated on appropriate media and identification was done by colony characteristics, staining by Grams method and specific biochemical tests. Antibiotic sensitivity pattern was determined on isosensitivity agar by Kirby Bauer method. Colicin production was determined by the method of Djønne.

Results
Among 100 strains of *E. coli*, 7 % (n= 7) showed Colicin production. Antibiotic sensitivity pattern of colicin producing strain showed sensitivity to gentamycin only and resistance to sulfamethoxazole/trimethoprim, amoxicillin/clavulanic acid and chloramphenicol. 10 strains of Pseudomonas spp. and ten *Enterobacter* spp. isolated form clinical specimens were colicin producers.

Conclusion
Colicin production was observed in uropathogenic *E. coli*. As colicin producing strains were resistant to most antibiotics it may colonize and cause persistent infection.

Key words
Inhibitory activity, Colicin, Clinical specimens

Introduction
Colicins are toxin released through plasmids which show inhibitory activity against *E. coli* and other bacteria.[1] Production of colicin occurs in high amounts and is released into the extracellular site.[2] Colicins are a group of bacteriocins which have antimicrobial properties and 30 % of *E. coli* can produce one type of colicin. Bacteriocin can play a vital role in colonization of *E. coli* in the gastrointestinal tract. The capability to produce bacteriocins can be an important factor in determining the establishment of probiotic *E. coli* in the gastrointestinal tract of humans and animals.[3] Inhibition of catheter colonization by uropathogenic *E. coli* can be attributed to the presence of a colicin-producing strain of *E. coli* on the catheter surface. Bacteriocin production by non-pathogenic organism might prevent catheter-associated UTI as colicins inhibits colonization of urinary catheters.[4] *E. coli* produces two types of bacteriocins, microcins and colicins. Microcins were prevalent among non-multidrug-resistant strains compared to multidrug-resistant strains. Microcins contribute to virulence of *E. coli* and cause bacteremia of urinary tract origin.[5] Colicins are typically produced under stress conditions and classified according to their mode of action or pathways. Colicins are capable of inhibiting E2 and *E. coli* 157 H7.[6] Gram negative bacteria isolated from poultry indicated that only one R plasmid showed colicin production.[7] Colicin K demonstrated distinct inhibitory activity to uropathogenic *E. coli*. Low prevalence of colicin K and high prevalence of Col E1-like plasmids were observed among uropathogenic strains.[8] Colicin E1 appears to be a virulence factor of certain uropathogenic *E. coli*.[9] Bacteriocins are suggested for cancer treatment[10] and have been tested as a drug for AIDS.[11] This study was done to isolate colicin producing *E. coli* and to determine its inhibitory activity against other *E. coli* or closely related bacteria.

Methods
One hundred *E. coli* strains from different clinical specimens and food samples were collected. Clinical specimens were urine (52), pus (10), wound swab (6), vaginal swab (5), stool (3), aspirate (2) and twenty *E. coli* strains were isolated from different food samples. 20 strains of *Pseudomonas* spp. and *Enterobacter* spp. were also collected from other clinical samples. Bacterial strains were inoculated on appropriate media and identification was done by colony characteristics, staining by Grams method and biochemical tests. Antibiotic sensitivity pattern against gentamycin, sulfamethoxazole/trimethoprim, amoxicillin/ clavulanic acid and chloramphenicol was determined on iso-sensitivity agar by disk diffusion method of Kirby Bauer and zone size was determined according to CLSI guidelines.

Detection of colicin production was determined by a modified method of Djønne.[12] Spot cultures of producer strains were

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grown on Blood agar plates and incubation was done for 48 hours at 37^0C. Plates were later exposed to chloroform vapors for 30 minutes at room temperature. Colicins are resistant to chloroform while bacteria are sensitive. Excess chloroform was removed and plates were left undisturbed for 30 minutes at room temperature to remove residual chloroform.

Producer strains were tested against various antibiotics and after 24 hours of incubation, zones of inhibition were measured. The indicator strain used for determining colicin production was *E. coli* isolated from food samples. Indicator strains were grown on blood agar. One colony of indicator strain was mixed with 0.5 ml of sterile saline and overlaid on blood agar containing spots of producer strains. Excess saline was removed and the plate was left at room temperature for one to two hours. Incubation of the plates was done for 24 hours at 37^0 C. Zone diameter was measured and if more than 1mm, the strain was considered positive for colicin production. All 100 producer strains were tested for colicin with the indicator strains in similar manner. The strains which showed positive results for colicin production were also tested against 20 other strains of *Pseudomonas* spp. and *Enterobacter* spp.

Results

One hundred *E. coli* strains were analyzed for colicin production and two positive colicin producing strains were tested against 20 strains of *Pseudomonas* spp. and *Enterobacter* spp.

Figure1 shows the colicin producing strains of *E. coli*. Out of 100 strains 7 (7%) showed colicin production. Colicin production was found in 7/52 (13.5 %) of uropathogenic *E. coli* while no colicin production was detected from *E. coli* isolated from other clinical specimens.

Inhibitory activity of colicin producing strains of *E. coli* against *Pseudomonas* spp. and *Enterobacter* spp. is shown in Table 1. Colicin producing strains no.12 and no.18 were found to be resistant to all 10 strains of *Pseudomonas* spp. and 10 *Enterobacter* spp. isolated form clinical specimens.

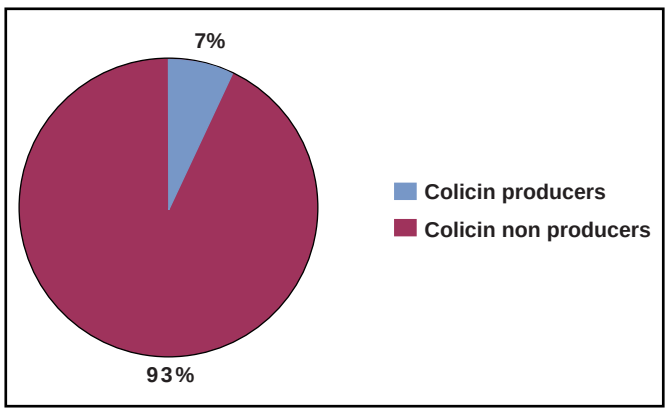

Fig 1. Detection of colicin producing strains of *E.coli*

Table 1. Inhibitory activity of colicin producing strains of *E. coli* **against** *Pseudomonas* **spp. and** *Enterobacter* **spp.**

Strains	Pseudomonas (10)	Enterobacter (10)
E.coli strain No 12	Resistant	Resistant
E.coli strain No 18	Resistant	Resistant

Discussion

Colicins producing *E. coli* are often isolated from clinical specimens and other *E. coli* from different sources. In the present study 7 % of uropathogenic *E. coli* were colicin producers.

Reports from a study in Brazil indicated that out of 100 uropathogenic *E. coli* 79% produced aerobatic, 69% showed serum resistance, 44% produced mannose-resistant hem agglutination (MRHA), 32% were beta-hemolytic and 22% were colicinogenic. A greater proportion of UTI *E. coli* strains produced anaerobatic, colicin V, beta-hemolysis and MRHA and the production of MR adhesions and hemolysin might contribute to the virulence of these strains.[13] A study conducted in Turkey on *E. coli* strains isolated from urine of patients in Izmir and Manisa indicated that out of 129 uropathogenic *E. coli 33* (25.5%) produced colicin. The strains produced 10 identical types of colicin. Among these colicin types, group E was more than 50%. Out of 129 *E. coli* strains, 22 (17%) produced colicin V.[14]

Resistance to antibiotics was observed in colicin producing strains of *E. coli* and only gentamicin was found to be sensitive. A previous report from Liaquat Hospital Jamshore, Pakistan indicated that organisms isolated in urine cultures were gram negative rods and that pathogens causing UTI were developing resistance against commonly used antibiotics.[15]

Conclusion

In conclusion it may be stated that colicin producing *E. coli* were uropathogenic and showed resistance to *Pseudomonas* spp. and *Enterobacter* spp. isolated from other clinical samples. Colicin producing strains may also be part of our normal flora. Loss of these harmless organisms by indiscriminate antibiotic use may allow the opportunistic bacteria to invade the human body. They house resistance genes and may transmit them to other pathogenic bacteria.

Acknowledgement

The practical work for this paper was conducted by Ms. Erum Habib (M.Sc student, Department of Microbiology, University of Karachi) under the supervision of Dr Rakhshanda Baqai who also contributed by writing this manuscript.

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CASE REPORT

Congenital Malaria – A Case Report

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Abstract
Congenital malaria is an uncommon disease in infancy. The burden is more in malaria endemic countries. We are reporting a case of a 24 day old neonate who admitted with fever and pallor and without other physical manifestations. Initial investigations were unremarkable except his peripheral smear was positive for *plasmodium vivax* trophozites. Although congenital malaria is rare, but screening is essential in endemic areas to prevent infant mortality and morbidity.

Introduction
Congenital Malaria is amongst the unusual infections encountered globally.[1] The worldwide prevalence of malaria accounts for more than 200 million people being infected yearly.[2] Even though in endemic regions of the Indian sub-continent and Africa, congenital malaria and malaria in pregnancy can be a disease burden, but in Pakistan it has yet not been extensively explored.[3] Proper awareness and appropriate management is required to prevent the mortality and morbidity accounted in this illness.[3]

Case Report
Twenty four days old male neonate was admitted in the neonatal unit of the Aga Khan Maternity and Child Care Centre, Hyderabad, with complaints of intermittent high grade fever, lethargy and reluctance to feed. He was born at full term pregnancy by normal vaginal delivery to a primigravida mother. Mother had history of fever with rigors in the 3rd month of gestation. On the 4th day of life the baby was admitted at another hospital due to bleeding per rectum and from the mouth and was treated as a case of hemolytic disease of the newborn. On admission, he was febrile with temperature of 39^{0}C; heart rate and respiratory rate were 145/minute and 52/minute respectively. He was pale but non-icteric. His anthropometric measures were normal. There was no visceromegaly and, cardiovascular and nervous system examinations were unremarkable. There was no Bacillus Calmette-Guérin (BCG) vaccine scar present on his right arm.

Complete blood count (CBC) and peripheral blood smear revealed microcytic normochromic anemia (hemoglobin (Hb) - 9.2 g/dL, mean corpuscular volume (MCV) – 84.9 fl, mean corpuscular hemoglobin concentration (MCHC) - 34.2 g/dL) and thrombocytopenia (platelet count – 17 x 109/L). The total leukocyte count (4.3 x 109/L) and differential count (Neutrophils – 42%, lymphocytes- 48% and monocytes - 08%) were unremarkable. Peripheral smear revealed trophozoites, gametocytes and schizonts of *plasmodium vivax.*

The baby was treated with chloroquine initially at a dose of 10 mg/kg (base) for two days followed by 5 mg/kg on day three. The patient was also transfused with packed cells and platelets. There was prompt relief from fever and improvement in cell counts. The patient remained stable, tolerated feed and had disappearance of *plasmodium vivax* on subsequent peripheral smears. Patient was discharged and was followed as an outpatient, was well and had no recurring complaints.

Discussion
In Pakistan, malaria is reported to be a highly prevalent disease with infections most commonly due to *plasmodium vivax* but there is an increasing occurrence of infections due to *plasmodium falciparum* reaching to almost 35-40% of the cases.[4] Since the initial account of congenital malaria, approximately a little more than 300 cases have been reported.[2] Congenital malaria is defined as symptoms occurring in a child within 10 to 30 days after birth varying from a day old baby to weeks or months of age. Malaria has considerable impact on overall disease burden on newborns with indirect effects on preterm labor leading to prematurity, intra uterine growth restriction and pregnancy losses. Despite these well-documented indirect effects of malaria to the fetus and newborn, the direct burden of neonatal malaria infection in terms of prevalence and outcome is not well described in malaria endemic areas.[5] Pregnancy is known to be common cause of relapse with *plasmodium vivax* due to natural immune suppression that is characteristic of pregnancy.[6]

In new borns, typical presentation of malaria may not be evident due to depressed erythropoiesis as a result of inadequate reticulocytes and the parasites causing malaria only use reticulocytes for replication.[7] More than 80% of the cases present with fever, anemia and splenomegaly along with other features such as drowsiness, restlessness, poor feeding, regurgitation, loose stools, jaundice and hepatomegaly.[7] The present case also shows that congenital malaria may present with non-specific symptoms of lethargy and refusal to feed in initial few days of life. Even with the widespread use of chloroquine in pregnancyas a preventive measure in a dose of 300 mg base/week, teratogenic effects have yet not been

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confirmed.[8] The established treatment for congenital malaria includes the use of chloroquine given at a dose of 10 mg/kg of body weight of base at the 1st and 2nd day, followed by 5 mg/kg on 3rd day with no use of primaquine due to the absence of the tissue phase.[8]

Conclusion

In endemic regions and in infants of immigrant mothers in developed countries, malaria should be suspected in any neonate with fever and anemia with splenomegaly. Early diagnosis and treatment could effectively prevent infant mortality.

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CASE REPORT

Progressive Multifocal Leukoencephalopathy in a Child with AIDS

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Abstract
Central nervous system (CNS) manifestations of human immunodeficiency virus (HIV) present later in the course of the disease and carry a very poor prognosis. Numbness, paraparesis, amnesia, meningitis, confusion and seizures are among the various presentations of involvement. We present a newly diagnosed child with HIV who presented with progressive confusion, cognitive dysfunction, upper motor neuron paraparesis and who later was diagnosed with HIV related progressive multifocal leukoencephalopathy (PML).

Key Words
HIV, Pakistan, Progressive multifocal leukoencephalopathy.

Introduction
CNS manifestations of HIV are varied and usually carry a very poor prognosis. PML is a focal demyelinating disease of the CNS characterized by widespread lesions due to infection of oligodendrocytescaused by reactivation of latent infection with human polyoma virus JC virus (JCV).[1,2] The virus has worldwide distribution, with a sero-prevalence of 39-69% among adults.[3] It occurs almost exclusively in immunosuppressed individuals including those with acquired immunodeficiency syndrome (AIDS) with almost 85% of the total cases and a prevalence of around 4-5%.[4] We present a child with diffuse PML and a review of current literature.

Case Report
A 13-year-old boy, student of grade 2, presented with 5 days history of weakness in both legs and inability to stand. He was well till 3 weeks back when he started having difficulty in remembering lessons at school but was able to recognize his relatives. This was followed by dysuria and dribbling of urine 2 weeks ago without hematuria or fever. For the last 5 days, he had been having difficulty in standing and bearing weight on his legs and the amnesia had progressed to confusion, inability to follow complex commands and slurring of speech. He had a fall with no loss of consciousness, vomiting or bleeding from the head. He had been receiving anti tuberculous medications for last one year for presumed abdominal tuberculosis. He also received blood transfusion for severe anemia (hemoglobin 4 gram/dl) in 2013. He was an orphan living with his uncle and aunt. Both parents died 7 years back from an undiagnosed acute febrile illness. His father was a taxi driver and his mother was a housewife with no history of travel abroad or blood transfusions. His birth history was normal and previous medical history was unremarkable except for recurrent febrile illnesses. His vaccinations were reported complete.

On examination, he was a sick looking child, lying in bed, alert but confused and disoriented in time and space. His heart rate was 123/min, respiratory rate 20/min, temperature 98°F, 98% oxygen saturation on room air and weighing 37 kilograms. His general physical was unremarkable except for non-tender cervical lymphadenopathy and oral thrush. His chest exam showed bilateral inspiratory coarse crepitations. His cardiovascular and abdominal exams were unremarkable. On his neurology examination, his Glasgow Coma Scale score was 14/15, his right pupil was not reactive and his right lateral rectus was paralyzed. He exhibited slurred speech but was able to understand words and communicate. He was able to follow two step commands but got confused with complex commands. His upper limbs were normal however both lower limbs showed increased deep tendon reflexes with up-going plantars. On fundoscopy, chorioretinitis and sclerosis of retinal vessels was observed.

Initial laboratory investigations showed white blood cell (WBC) count 3700/µL with lymphocytes 50%, hemoglobin 12.8 g/dl, platelet count 198000/µL, potassium 4.4mEq/L, chloride 106 mEq/L, bicarbonate 24 mEq/L, glucose 73 mg/dL, alanine aminotransferase 124 U/L, albumin 3.6 g/dL, blood urea nitrogen 7 mg/dl, urea 14.98 mg/dl, creatinine 0.64 mg/dl, and C- reactive protein 0.5 mg/l. A MRI of brain and thoracic spine with and without contrast showed post contrast enhancement of leptomeninges and hyper-intense signals diffusely scattered in the brain and cervico-thoracic cord (Figure 1, 2).

His HIV ELISA and HCV antibodies were positive. Further work up included cerebrospinal fluid analysis, with 20 WBC (neutrophils 20% and lymphocytes 80%), glucose 48 mg/dl, protein 59 mg/dl, LDH 31 U/L with fungal and AFB smears and India Ink negative. Other viral and parasitic serology (Hepatitis A IgM antibody, HBsAg, toxoplasma IgM, rapid plasma reagin and cytomegalovirus IgM) were negative. His serum LDH was 312 U/L and peripheral film showed few reactive lymphocytes as well. His chest x-ray showed bilateral diffuse haziness and non-homogenous nodular opacities.

With all of above findings, the patient was diagnosed to have AIDS with PML, concurrent HCV and opportunistic chest

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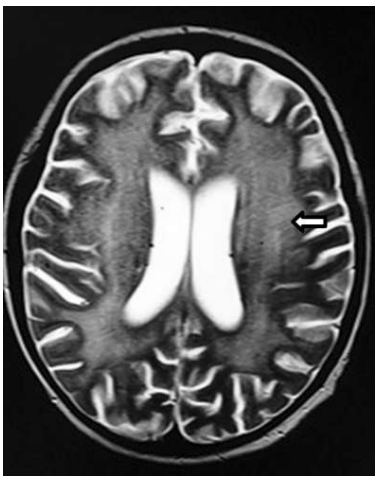

Fig 1. Axial T2- weighted MRI of brain showing bilaterallhyperintense signals in periventricular areas (arrow).

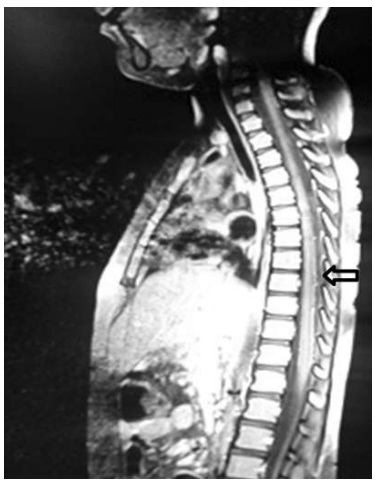

Fig 2. Post contrast sagittal MRI of dorsal spine showing enhancement of leptomeninges (arrow).

infection. The patient was started on intravenous fluids, broad-spectrum antibiotics, fluconazole, oral nystatin drops and co-trimoxazole/trimethoprim prophylaxis. He was referred to a HIV center in a public hospital for further testing (CD4 and HIV viral load) and anti retro-viral therapy (ART).

Discussion

PML is a very common infiltrative brain lesion seen mostly in AIDS patients with low CD4 (<200/µL) and is one of the AIDS-defining illnesses in these patients.[3,4] It is caused by reactivation of JCV due to suppression of the immune system. The JCV infects oligodendrocytes causing progressive demyelination of neurons in the central nervous system (CNS). The symptoms depend upon the areas of brain affectedand typically present with multiple focal deficits of the cerebrum and brainstem. Affected patients present with limb weakness, impaired speech, cognitive impairment, gait disturbance, seizures and visual abnormalities.[1,2,5] Our patient presented with lower limb paraparesis, confusion, slurring of speech, amnesia and inability to see from the right eye.

The differential diagnoses include infectious and non-infectious causes. The slow clinical progression over several weeks often provides a clue to the diagnosis. The major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral infarcts begin even more abruptly. In most cases of PML the combination of clinical and neuroimaging findings lead to presumptive diagnosis of PML. The definite diagnosis of PML is made on brain biopsy. As it is an invasive procedure, it has been replaced by other techniques like polymerase chain reaction (PCR) for JCV in CSF, neuroimaging along with CD4 counts.[1,5-7] Magnetic resonance imaging (MRI) is the investigation of choice due to its higher sensitivity. It is characterized by non-enhancing lesions in subcortical white matter with no mass effect, which are hyperintense on T_2-weighted and FLAIR magnetic resonance and hypointense on T_1- weighted MRI.[2,7] Our patient also showed similar findings on MRI of the brain and spine. However PCR for JCV is not available in our setup.

There is no effective antiviral therapy for preventing or treating JCV infections or PML. ART is the mainstay of therapy for JCV infection with boosting up of immune system and thus increased survival of these patients.[8]Therefore ART should be started immediately in a patient with PML. Certain other experimental treatments have been tried (cidofovir, mefloquine, cytarabine, topotecan, interferon-alpha, and inhibitors of the serotonergic 5-HT2a receptor) but have no proven benefit and are not recommended.[9,10]

PML has a progressive and fatal course. Less than 10% of patients with HIV and PML survived longer than 1 year before the advent of ART.[5] However, 1 year survival rate has increased up-to 50% in the era of ART.[5] Re-myelination does not occur in the affected brain areas and serious neurological defects are seen in up-to 80% of PML survivors.[5] There is no known prevention.

Conclusion

PML should be suspected in an immunocompromised child with progressive CNS manifestations. Therapy should be directed to preserve immune function or reverse HIV-associated immunosuppression with effective ART.

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A Family Cluster of Pulmonary Tuberculosis

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Abstract
Multi drug-resistant tuberculosis (MDRTB) is caused by certain strains of *Mycobacterium tuberculosis* complex that have acquired chromosomal resistance to Isoniazid and rifampicin, which are the most important first line anti tuberculosis drugs. It is either acquired during the course of the patient's treatment due to inadequate therapy, or may occur as a primary infection. Transmission of TB can be prevented by appropriate and complete treatment of the disease, and by educating patients and families on respiratory secretion precautions.

We report a case of an elderly gentleman with MDRTB diagnosed via GeneXpert and sputum culture. Ten other family members, who shared the same home, acquired TB, most likely through not observing proper precautions.

Case History
A 70-year-old gentleman (patient A, Fig 1) presented to the outpatient clinic at The Indus Hospital Karachi, in 2012, with a 6 week history of fever, hemoptysis and cachexia. The patient had a positive history of exposure to multi drug resistant tuberculosis from his nephews who lived with him in the same house, and whom he took care of during the course of their disease. He was a non smoker and did not consume alcohol or illicit drugs. He tested negative for HIV and had never been treated for TB in the past.On the basis of the results of the sputum culture and sensitivity tests, the patient was diagnosed with MDR pulmonary tuberculosis. Drug sensitivity testing showed resistance to isoniazid, rifampicin and ethambutal, and sensitive to levofloxacin, ethionamide, cycloserine and amikacin. He is being treated with individualized treatment regimen under a DOTS Programmatic Management of MDR TB (PMDT), at the Indus Hospital Karachi. At the Indus hospital, adherence to therapy is ensured through having a supporter for each patient, whereby the supporter visits the patient each morning, and administers the injection and the pills. He/she also enquires for adverse events or any unusual circumstances that may impede the patient's care, and reports back to the treating physician. Each patient also receives a monthly food basket with essential nutrients sufficient for a month.

The patient's family history revealed that ten other members in his family were also diagnosed with pulmonary tuberculosis. His brother's wife (patient X, Fig 1.) reportedly contracted tuberculosis from her neighbors in 1996. Her sputum smear or culture were unknown, but she was given Category I treatment (Table 1.) with rifampicin, ethambutol, pyrazinamide and isoniazid. The treatment was not supervised and she defaulted during the course of her treatment and died at the age of 35 in 1999 due to unknown causes.

Patient X's husband (Patient D, Fig 1) and their family of six children, and three other adults lived in a congested hut, which consisted of a single room with a single window. Patient D and their four oldest children eventually acquired the disease. All of them were given Category I treatment. Patient D died at the age of 45, while the four eldest children (patients E, F, G, H, Fig 1) who were presumably infected, with the same strain passed away between the ages of 20-25 between 2001-2003. They had received questionable treatment, and sputum cultures were not done, but could possibly have MDR TB, acquired from Patient X who had defaulted on therapy.

Patients X and D's two sons (Patients I, J, Fig 1) were diagnosed with MDR TB in 2004 at the ages of twenty and twenty two. They were treated with second line drugs for tuberculosis. The drug sensitivities, names or dosages of the medications are not known to us. However, they did not comply with the treatment, and both died within one year of their diagnosis at ages of twenty two and twenty four in 2006 and 2007 respectively from their disease.

The two youngest children infected their uncles and aunt

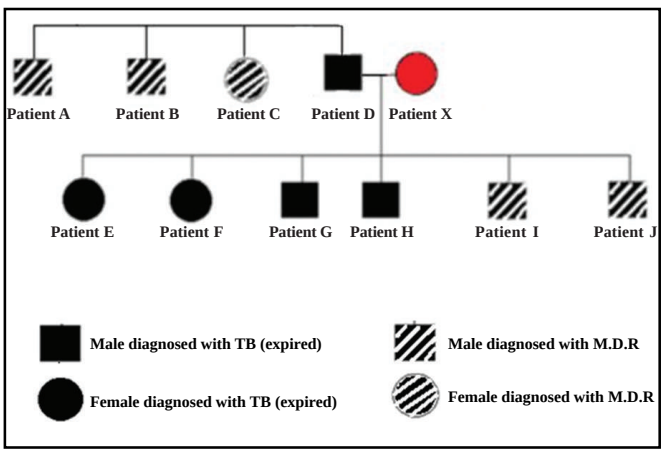

Fig 1. The Family tree showing the spread of MDR TB within a family from a single source case.

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(Patients A, B, C) who were their caretakers at the time of illness, were infected by their nephews who would not comply with proper tuberculosis preventive practices such as wearing masks, following proper cough etiquette, or sleeping in separate quarters. Patient B was treated with cycloserine, levofloxicin, PAS, capreomycin, pyrazinamide and ethambutol, and he successfully completed treatment within 2 years under the DOTS program. Patient A and C were last followed in 2013, during which they were undergoing treatment under the DOTS program for MDR-TB. Neither patient reported any side effects to their treatment.

Discussion

Tuberculosis is spread through airborne particles, called droplet nuclei. These particles are generated when a patient infected with pulmonary or laryngeal tuberculosis, coughs, or sneezes. These droplet nuclei harbor infectious strains of *Mycobacterium tuberculosis*. Each particle is around 1-5µm in size and may remain airborne for long periods of time and may spread throughout a building or room.[2] A person gets infected by inhaling droplet nuclei harboring *M. tuberculosis*, through the nasal cavity, which reach the alveoli by passing through the upper respiratory tract and bronchi.[3]

Persons sharing the same airspace as the infected individual for prolonged periods of time, with poor ventilation of the room causing inadequate dilution of the particle or removal of the infectious airborne particles, have the greatest risk of being infected.[4, 5] In our case the patient X and her family of six children and three other relatives, who came from an impoverished background, all slept in close quarters in the same bedroom which had only a single window; hence the room had poor ventilation, resulting in poor air circulation.

Table 1: Treatment Regimens for Tuberculosis

Treatment category	TB treatment regimen	
	Intensive phase	Continuation phase
I	2 (HRZE)	4 (HR)
II	2 (HRZES) followed by 1 (HRZE)	5 (HRE)

Key= H: Isoniazid; R: Rifampicin; E: Ethambutol; S: Streptomycin; Z: Pyrazinamide

Category I New cases
Category II Re-treatment

Category I patients: In the intensive phase patients are treated with a combination of four 'first-line' drugs: isoniazid, rifampicin, pyrazinamide and ethambutol for two months, 2 (HRZE). In the continuation phase, they are given a combination of isoniazid and rifampicin for four months 4 (HR)

Category II patients: In the intensive phase patients are treated with five drugs during the first two months: a combination of isoniazid, rifampicin, pyrazinamide and ethambutol 2 (HRZE), in addition to streptomycin (S); then continue with four drugs, excluding streptomycin, for an additional one month; then followed by five months of the continuation phase with isoniazid, rifampicin 5 (HR), and ethambutol (E).

We did not know Patient X's drug regimen, and neither did she complete treatment. Consequently, we assume she may have developed drug resistance and transmitted to the rest of the family. Five of the eleven members of the family (A, B, C, I and J) had MDRTB, whereas six persons (X, D, E, F, G and H) had not had cultures, but may conceivably have had drug resistance and died. One of the factors that resulted in the spread of MDR-TB from patients I and J to their caretakers, patients A, B, and C was the fact that the infected individuals would not comply with basic techniques to prevent transmission of their disease. Patients I and J refused to wear masks around their relatives and at home; they would openly cough in the direction of their caretakers and would refuse to turn their heads in the opposite direction as no one had educated them about proper cough etiquette. Research has shown that patients who are suspected, or are confirmed cases of smear positive tuberculosis could effectively reduce transmission of infection by practicing proper coughing etiquette, or by wearing a mask (5). While coughing, the patients should be instructed to cough into their elbows, and to cover their mouth and nose with their hands, or a piece of cloth or tissue paper.[6]

Another factor that further potentiates the risk of infectiousness in an already infected individual is inadequate or incomplete treatment.[7] This fact was demonstrated in our case as Patient X initially showed improvement while on ATT but her condition worsened after she discontinued her treatment, and subsequently resulted in spread of the disease to her husband and children, all of whom took their medications irregularly, which spread the disease to Patients A, B and C. However patient B, who was diagnosed with MDR tuberculosis, was successfully able to complete his treatment after strictly adhering to his drug regimen for two years. However it is interesting to note that not all individuals exposed to *M tuberculosis* get infection, and more over progression to clinical tuberculosis only occurs in 10% of those infected with the bacteria. Genetic predisposition is thought to play a major role in susceptibility to tuberculosis. A mutation in NRAMP-1 plays an important role in the host's innate response to infections, and is thought to predispose individuals to tuberculosis.[8]

To effectively contain the spread of tuberculosis there is a need to implement a framework that addresses both the patient's clinical and socioeconomic issues. In view of these issues the World Health Organization's (WHO) Directly Observed Treatment short-course (DOTS) strategy aims to implement cross country standardized treatment regimens.[9] Through the DOTS program the patients should receive supervised treatment,

whereby their supervisors ensure that they are taking their medication regularly, and eventually follow treatment to completion. The appointed supervisor should preferably be one who is acceptable to the patient and is trained and supported by a medical institution.[10]

The Stop TB Strategy is a program initiated by the WHO, which aims to reduce the global burden of tuberculosis by 2015. A component of this strategy is to limit the spread of MDR-TB through early detection and its subsequent treatment. It is recommended that routine diagnostic drug susceptibility testing (DST) be carried out on all TB patients, in order to monitor trends in drug resistance and outbreaks that would otherwise go undetected. However, in countries where routine DST is not accessible, special surveys are being carried out. These drug resistance surveys reduce laboratory workload in poor resource areas by incorporating the use of molecular screening tests such as GeneXpert MTB/RIF. By detecting the resistance gene of the organism to Rifampicin, this technique can identify cases of possible MDR-TB and lead towards early treatment.[11]

However the main strategy to control tuberculosis is educating the patients and their families on how to prevent the further spread of tuberculosis. Those receiving treatment must be informed about the importance of adhering and completing treatment in order to prevent the development of drug resistant strains of tuberculosis.[12]

Conclusion

Eleven persons in the same household acquired pulmonary tuberculosis, six of whom defaulted during the course of their treatment with Category I drugs. Two patients with proven MDR TB defaulted on second line drugs. The infection was passed on further to three other family members, the caretakers of the deceased who were also diagnosed with MDR TB; one family member has already completed treatment with second line drugs, while the other two were receiving second line drugs for treatment until their last follow up in 2013.

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11th Annual Conference on Infectious Diseases

Medical Microbiology and Infectious Disease Society of Pakistan (MMIDSP) organized the 11th Annual Conference on Infectious Diseases in Islamabad on 14th- 15th March 2014.

Addressing a large gathering of health professionals at the inaugural session, the chief guest Dr. Jehanzeb Aurakzai, DG Ministry of National Health Services, regulations and coordination said that "This big gathering of scientists, microbiologists and infectious disease experts and young researchers will help to share among each other vital statistics on infectious disease. We know that in Pakistan public health has always been a challenge. We in Pakistan have to understand our endemic diseases and formulate our own health needs. No other factor in disease control is more important than awareness, followed by intervention". He further lauded MMIDSP for starting the initiative of "Antibiotic Stewardship Initiative in Pakistan (ASIP)". He said this was a timely and great service and he assured all support on behalf of the Government of Pakistan in this context.

Dr. Ejaz Khan, President MMIDSP and Chairperson of Organizing Committee, Consultant Pediatrician, Shifa International Hospital welcomed the attendees and pointed out, "The issue of global challenge of antibiotic resistance is monumental, with almost all countries and regions being affected, including Pakistan. We know very well that 'antibiotic misuse and overuse' have contributed tremendously to a major health crisis within Pakistan. Antimicrobial stewardship aims to improve appropriate prescription of antibiotics in all healthcare settings. MMIDSP plans to launch an "Antibiotic Stewardship Initiative in Pakistan (ASIP) at this conference by inviting all stakeholders".

Dr. Aamer Ikram, leading microbiologist and secretary of the conference said that, "This is an excellent opportunity to exchange information with both national and international experts".

Speaking as keynote speaker on "Antibiotic Stewardship: A new buzzword and launch of antibiotic stewardship initiative in Pakistan" Dr Naseem Salahuddin (Consultant infectious diseases Indus Hospital Karachi and past president MMIDSP), spoke about its aims and objectives. She said "There is a dramatic increase in the prevalence of superbugs, and there is an equally drop in the number of available antibiotics. Bugs have developed their own weaponry to fight chemicals and not the other way around. We have homegrown MRSA, VRE, ESBL, NDM, and many more with escalating MICs." She lamented, "We have overused antibiotics in the community. A scratchy throat, a cold, or a bit of diarrhea, are almost always of viral origin, and yet the sufferer is prescribed an antibiotic or two plus a bagful of multivitamins, antipyretics and probiotics." About ASIP she envisioned that "It needs strong support and endorsement from professional societies, medical colleges, WHO, PMA, Ministries of Health, Drug Regulatory Authority, PMRC and others, to make this transformation which will lead to better patient care". She further said, "A task force will be formed with representation from leaders and policy makers of different government and private organizations and recommendations presented to decision-making authorities. A declaration will be made after further debate and discussion."

The content of the conference was broad and comprehensive that highlighted the burning infection issues in Pakistan. Sessions with free papers on *Antimicrobials & Resistance, Tuberculosis, Molecular Biology and emerging infections* were conducted with more than 500 participants. The participating speakers for the conference were Dr. Altaf Ahmed, (Consultant Microbiologist at Indus Hospital Karachi and past president MMIDSP), Dr. Babar Cheema (Pulmonologist and Infectious Disease expert Military Hospital, Rawalpindi), Dr. Ejaz Qadeer (Manager National TB Program), Dr. Amjad (National TB Program) and Dr. Afia Zafar (consultant Microbiologist Aga Khan University Karachi). The preconference four workshops included, "*Antibiotic Stewardship*," "*Pediatric Tuberculosis*," "*Infection Control*" and "*Scientific Manuscript Writing*." These workshops were a resounding success with >350 participants. Moderators and experts conducted these workshops with active participation from the enthusiastic audience. The conference received full and enthusiastic participation. Overall around 170 abstracts were received for oral and poster sessions.

At the concluding ceremony three travel grants and cash prizes for 6 best oral and poster presentations were awarded as well. Dr. Aamer Ikram thanked the audience, speakers, authors, volunteers, organizing committee and the pharmaceutical companies for their role in making this a successful conference. It was decided to hold the 12th Annual Conference of Infectious Diseases in Karachi in spring in 2015. There were many congratulatory comments for holding a very successful and well-attended meeting.

Master Class in Respiratory Diseases, 18th May 2014

Shifa Tameer Millat University and Shifa International Hospital, Islamabad in collaboration with Society for Advancement of Medicine and Medical Microbiology, National TB Control Program and Medical Microbiology and Infectious Disease Society, Pakistan (MMIDSP) held a "Master class in Respiratory Diseases", on Sunday 18th May 2014, 9am to 6pm, at Aiwan e Quaid, Nazriya Pakistan Council, Islamabad. The aim of this intensive and interactive meeting was to review the preventive and therapeutic aspects of some current issues in respiratory diseases. It was a very well attended session by ~280 participants including general practitioners and other physicians, nurses, technicians and students from the twin cities of Rawalpindi-Islamabad.

After Tilawat, Dr. Saeed Ullah Shah welcomed the guests and spoke on idea behind these Master classes, which was the fifth in a row. The first talk was by Dr. Aftab Akbar, Pulmonologist from SIH was on *"Diagnosis and management of Obstructive Airway Disease"*. He spoke about how a physician must take a detailed history and perform a thorough physical examination along with laboratory evaluation in obstructive airway disease. He also highlighted some key management issues. This was followed by a talk by Dr. Mati-ur-Rehman, Pulmonologist and NTP Advisor for DRTB who lamented the *"Hazards of Smoking"* and gave important cessation strategies. Dr. Ejaz Khan, President MMIDSP, Pediatrican and pediatric ID specialist at SIH, shared developments and ongoing research in *"Childhood Respiratory Infections"* including new and evidenced based therapies for common infections such as pneumonia, otitis media, sinusitis and TB. In his talk *"Adult Respiratory Infections"* Dr. Ghulam Haider Khalid from SIH discussed the role of physicians to arrive at a specific adult respiratory infections diagnosis. He also emphasized the outpatient management of common diseases such as pneumonia and bronchitis. Dr. Kamran Rashid from Oncology Department SIH then followed with *"Diagnosis and Management of Lung Carcinoma"* and elaborated how to pick early cancers and refer for definitive diagnosis.

After the lunch interval Dr. Suhail Naseem talked about *"Diagnosis and Management of Interstitial Lung Diseases."* NTP Manager, Dr Ejaz Qadeer highlighted the "Situational Analysis of TB in Pakistan!". He particularly asked the GPs to play their role in eliminating the scourge of TB from Pakistan.

A second talk by Dr Mati Ur Rehman, *"Diagnosis and Management of Tuberculosis"* ensured that the audience are interacted and stay abreast to participate fully. A very concise and snippy talk on *"Radiology of the Chest"* by Dr. Immad, Radiologist from SIH was highly regarded by the audience. Lastly preventive and therapeutic aspects of *"Obstructive sleep Apnea"* by Dr. Suhail Naseem rounded the daylong session.

There was active participation from the enthusiastic audience in the question and answer sessions that followed each session. Educational material was also distributed among the audience. Overall this master class was regarded as a success with current updates and topics of interest.

PIMA Meeting with MMIDSP (Theme *"Antibiotic Stewardship"*)

MMIDSP had an Infectious Disease session at the 23rd Biennial International Convention by Pakistan Islamic Medical Association, held at Convention Center, Islamabad on April 6th, 2014. MMIDSP was invited as one of the societies and was honored to have been invited at the august gathering.

The 2 hour session had about >150 participants and was chaired by Dr. Matiur Rehman (Pulmonologist, Advisor MDR TB, NTP) and co-chaired by Dr Altaf Ahmed (Indus Hospital, Karachi).

The first speaker, Dr. Ejaz A. Khan, President MMIDSP lamented the *"Use and Abuse of Antibiotics"*, he showed a number of "bad" prescriptions that highlighted the callousness of all physicians in prescribing antibiotics for every fever, cough, URI and diarrhea. He specifically talked about the evidence against antibiotics for common viral infections where antibiotics are not warranted at all. He pleaded to the physicians to curtail antibiotic misuse.

Dr. Matiur Rehman spoke on *"Situational Analysis of TB in Pakistan!"* and urged everyone to join hands and participate in NTP (National Tuberculosis programme) activities. He gave the latest figures on TB in Pakistan and talked about new TB recommendations from WHO. He also pointed out that now GeneXpert is available for rapid diagnosis in a lot of places within the country and NTP will extend its use to outreach areas as well.

Dr Altaf Ahmed gave his key messages in his introductory talk "Antibiotic Stewardship: An Urgent Need". He discussed how antibiotic misuse and overuse have contributed tremendously to a major health crisis with emergence of new super bugs, such as the dreaded carbapenem resistant *Klebsiella pneumonia*, *MRSA* and *NDM-1*. There is thus an urgent need to curtail their spread. He gave a brief review of antimicrobial stewardship: why, who, when, where. He said that in Pakistan tackling antibiotic misuse through antimicrobial stewardship will be an equally daunting and challenging task. Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) plans to address ASP (Antibiotic Stewardship) at both institutional and community levels by launching an "Antibiotic Stewardship Initiative in Pakistan (ASIP)". He asked everyone to join hands in the efforts.

In his *"ID Quiz / Interesting Cases"* Dr. Ejaz A. Khan had an interactive talk with input from the audience who were very attentive and knowledgeable.

After the session, the Chair congratulated the organizers for holding such an excellent and splendid meeting. Certificates and shields were distributed for participants and speakers at the end. An MMIDSP desk was set up at the occasion where education material for ASP was distributed and many participants were enthusiastic to join MMIDSP.

Research Misconduct and Recommendations for its Control

Dear Chief Editor,

Research is a fact finding profession and it must be impartial, objective and unbiased and data analysis and reporting ought to be free from any fraud, deceit and misconduct.[1] There are several dynamics which gives impetus to the researcher and allures them to endeavor in the research arena. The more successful the publication and specially in prestigious journal, the additional the chances of promotion, an attractive curriculum vitae, possible sponsorship, reward in shape of financial remuneration, pecuniary benefits, salary, social benefits, organizational, regional and national acknowledgment and recognition, respect, praise, and media publicity. All these rewards attract researcher to fabricate and falsify data finding in such significant way which achieve this all.[1-5] Researchers can not shield themselves from internal and external dynamics which could influence their intention to fabricate or manipulate their data. They shall not only be cognizant to those influences but each effort should be made to resist that temptation and represent the data impartially, honestly and the result should be present in the most accurate technique.

According to the German research funding body, there are two types of research misconduct namely; data falsification and fabrication.[6] In addition, several other aspects in research reporting are also considered as unethical and can be grouped under research misconduct such as incorrect reporting of missing data points, not reporting negative finding, reporting results of inappropriately applied statistical test, data mining, fishing and data scooping and exaggerating of results.[7] Data fabrication is defined as making up data or results and recording or reporting them.[5] It is also defined as the process through which researcher produce their data to mislead people without any actual work.[2] Fabrication is the more serious form of misconduct as it is comparatively easy for researcher to fabricate the data to their advantage and make it published. It will be actually impracticable for editors to distinguish fraudulent data. On the other hand, falsification is manipulation of research materials, equipment, process, or changing or omitting data or results[5] or reporting of data or information never present.[8]

A conventional way to identify research misconduct in data via audit and monitoring is an effective way, yet not only expensive, laborious, nonetheless near to impossible to verify all data. A random selection of data and auditing of analyses in articles presented for peer review and in addition methodical examination of peer review will not only be practical and productive but could possibly be serve as deterrence.[9] Raw and original data should be available to public access and funding institution should make it compulsory to researchers that all raw data should be made available on their websites.[2] Usually when data is fabricated it gets through some statistical test but they are possibly falling short on other test therefore such statistical tools and methods should be applied on raw data to find any fabrication or falsification in results. Univariate methods could be used to check the missing data.[10]

More importantly, the process of peer review is a grave process and should be performed fastidiously and must be devoid of prejudice, injustice, and free of bias. Reviewer must be able to vouch for conduct this process with honesty and with no intention of sabotage. Open review should be encouraged and adopted. While doing this, accountability and transparency should be maintained and followed. Continuous education on code of ethics and training the researcher to adhere to ethical standards should be promoted. It might be said that education has little or any effect on minimizing research misconduct as integrity comes from within; nonetheless this approach is being considered. Keep surveillance and control over funds flow of money and sponsors of research.[3]

Each author should be accountable for each and every aspect of their published paper and co author shall not be exonerated for any falsification or fabrication on behalf of the chief author. Moreover, it should be conditioned that each author should have contributed in protocol, data collection and analysis, writing publication and should have approved the final version. There should be specific validation system for all data,[1] enquiry into the sponsorship of the study and the flow of the money should be made transparent. This way the probable influence would be evident to every one. Also, if the system fails to recognize so the reader must be attentive.[11] It will thwart researcher intention from any kind of misconduct if they are sentient. Equal importance should be give to negative finding as given to positive finding. So the research is not enticed to fabricate or falsifying the result[8] as the journal is also an accomplice of misconduct by failing to consider negative studies.[10]

The Researcher must be cognizant of all rules regulations and consequences of infringement.

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Instructions to Authors

Scope

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

Criteria for publication

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

Submission of the Manuscript

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

Manuscript Categories

I. Original Articles

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

Title page

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

Abstract

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

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

Background

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

Materials and Methods

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

Results

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

Discussion

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

Acknowledgments

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

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

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

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

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

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

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

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

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

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

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

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

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

Instructions updated - April 2012.
Editor IDJ