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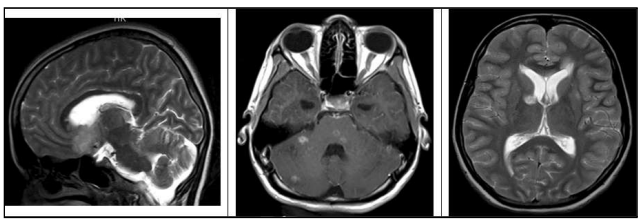

MRI brain: multifocal acute infarctions with multiple small tuberculomas within the brain parenchyma involving both supra and infratentorial compartments.

Courtesy: Dr Ali Faisal Saleem, Aga Khan University, Karachi.

New diagnostic tools for TB and their utility in a developing country

The importance of diagnosing both pulmonary and extra pulmonary tuberculosis cannot be overstated. The situation is even more important in countries like Pakistan which stands 5th among TB high burden countries and 3rd among MDR TB.[1] With a very high burden of drug resistant TB there is a huge requirement to diagnose TB rapidly and accurately for drug resistance and to control multi drug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB). An accurate, affordable and rapid test for the diagnosis of TB and determination of drug resistance is therefore a global priority.

To run an authentic TB diagnostic service there are some core components which must be fulfilled as stated by WHO. These components are sufficient funding, adequate human resources and training, country-specific diagnostic algorithms, appropriate infrastructure with bio-safety and bio-security, specimen transport and referral mechanisms, equipment validation and maintenance, management of laboratory commodities, laboratory information management systems and laboratory quality management systems.

Currently, the WHO recommended tests being used commonly in Pakistan are sputum smear microscopy by ZN or LED (light-emitting diode) methods, identification and drug sensitivity testing by both solid and liquid based culture and nucleic acid amplification test (GeneXpert) and line probe assays.

Pakistan National TB Control Programme (NTP), like in other low- and middle-income countries, still relies predominantly on sputum microscopy for diagnosis. It is cheapest among all tests and does not require extensive training. The method is not highly technical but the result depends upon the quality and bacterial load of the sputum specimen, training and motivation of laboratory technicians. In the best of centers it detects roughly 50% of active cases of TB and sensitivity can be as low as 20% in children and HIV-infected people. The introduction of fluorescent (LED) microscopy has increased the sensitivity of smear microscopy by barely 10% in some centers. Furthermore, smear microscopy cannot detect resistance to drugs and does not differentiate live from dead bacilli. Laboratory capacity to conduct sputum smear microscopy is still deficient. Pakistan has less than one centre per 100 000 population.[2] In Pakistan private health care set up has an important role in diagnosis and management of TB but the quality of services offered except for few is not up to the mark. In a recent study, sputum smear microscopy services in private laboratories of Karachi were found to be of poor quality with variations in results.[3]

The gold standard to obtain confirmation of TB is culture of Mycobacterium on liquid or solid media. It is more sensitive for TB diagnosis than smear microscopy and is used for testing both first and second line drug sensitivity.

There are automated systems for the growth and detection of mycobacteria with the capacity to incubate and continuously monitor mycobacteria growth indicator tubes every 60 minutes for increase in fluorescence. Growth detection is based on the AFB metabolic O_2 utilization and subsequent intensification of an O_2-quenched fluorescent dye contained in a tube.

However there are limitations as it has bio-safety requirements such as negative pressure facility, bio-safety cabinets, trained staff, and uninterrupted electricity with backup that are expensive to build and maintain and require engineering support. In Pakistan TB culture and drug sensitivity laboratories are few in number. The gap still exists to fulfill these requirements.

In 2010, a rapid and fully automated nucleic acid amplification test Xpert MTB/RIF was endorsed by the World Health Organization's Stop TB Partnership as the recommended initial diagnostic test (i.e. to replace sputum microscopy) in individuals suspected of having MDR-TB or HIV-associated TB. But unlike sputum smear microscopy, which has poor sensitivity in HIV-positive people, or sputum culture, which takes many weeks to give its results; this test detects *Mycobacterium tuberculosis* and resistance to rifampicin, within two hours. Globally, eighty eight countries are now using this system. The MTB/RIF assay is comparatively simple to perform with minimal training, is not prone to cross-contamination, requires minimal bio-safety facilities, and has a high sensitivity in smear-negative tuberculosis. However electricity fluctuation, high temperature and samples mixed with blood may result in invalid results.[4]

Molecular line probe assays (LPA) is also recommended by WHO for 1st-line anti-TB drugs, however sensitivity of INH is only 70%.

IGRA (Interferon Gamma Release Assay) and TST (Tuberculin Skin Sensitivity) tests detect latent TB infection by detecting immune response to TB bacilli. These tests are not capable of differentiating latent TB infection from active disease, and so are not recommended for diagnosis of active disease in high burden countries because of poor specificity.

Other tests being used are the nitrate reductase assay (NRA), thin-layer agar (TLA) color test, the microscopic observation drug susceptibility assay (MODS), the colorimetric redox indicator (CRI) method and phage-based assays.[5, 6, 7] These methods can detect MTB and resistance to INH and RMP. Among these MODS, NRA and CRI have been endorsed by the WHO, but TLA and phage-based assays have insufficient evidence for recommendation.

WHO guidelines strictly prohibit the use of commercially available sero diagnostic tests for diagnosing TB. There is yet

no evidence that existing commercial serological assays improve patient outcomes. Futher, high proportions of false-positive and false-negative results may have an adverse impact on the health of patients.[8] Inspite of WHO warnings, a number of serological tests are available in our market, draining the resources of already impoverished people. There should a strong legislation to stop the import and use of low quality test kits for purchase and use in our country.

In the Eastern Mediterranean Region (EMRO), Pakistan and Afghanistan have the highest burden of TB. Therefore top priority should be given to promote prevention, quality TB diagnosis, and treatment with quality medicines in both countries. The crisis can only be solved if all stakeholders work together to support efforts.

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ORIGINAL ARTICLE

Sources of Infection in a Tertiary Care Neonatal Unit and Role of Fumigation and Disinfection

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Abstract

Environmental contamination is a major concern for nosocomial infections in neonatal units. Sources of contamination are multiple and contamination with pathogens occurs during routine medical care. Coagulase negative *Staphylococcus* is a common nosocomial pathogen followed by *Bacteroids*, *Klebsiella* and *Pseudomonas* species. This study was designed to find out the potential sources of infection in our set-up and role of various methods in its eradication.

Methods
This is cross sectional study and conducted at Neonatology Unit of the Children's Hospital & the Institute of Child Health, Lahore from March 2007 to October 2012. We obtained samples for culture from air, liquid materials like oxygen flow meter water and solid materials like equipment, walls and windows of the unit before and after disinfection and fumigation with formalin solution and carbolic acid. Data was entered and analyzed in SPSS 16. Chi square test was applied to determine the significance and p value < 0.05 was considered as significant.

Results
Total 556 cultures were taken from various environmental sources. In the pre fumigation and disinfection stage 227 out of 288 cultures were positive while only 94 isolates were detected from 268 samples after fumigation and disinfection.(P=0.05) Microorganism detected from different sources were *Staphylococcus epidermidis* (n=96) followed by *Bacillus spp.* (n=67), *Klebsiella spp.* (n=59), *Staphylococcus aureus* (n=32) and *Pseudomonas spp*. (n=29).

Conclusion
Pathogenic microorganisms were isolated from various sources of neonatal ward and were potential reservoirs for nosocomial infections. Environmental disinfection and fumigation was effective in reducing their burden. However fumigation was unsuccessful in disinfecting the environmental air.

Keywords
Infection, Neonatal unit, Fumigation, Disinfection

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Introduction
Hospital acquired infections cost significantly in terms of morbidity and mortality of neonates.[1] Environmental contamination is major concern for nosocomial infections in neonatal units.[2] Sources of contamination include air, hands of health care providers, equipment, surfaces of walls & windows, suction machines and apparatus. Liquid medium like water in oxygen and air flow-meters, suction bottles, floor cleaning solution have a high likelihood to be the carrier of these pathogenic microorganisms.[2,3] Contamination with pathogens commonly occurs during routine medical care. Many studies have described the transmission of pathogenic organisms through contact with contaminated room surfaces.[4] Coagulase negative *Staphylococcus* is a common nosocomial pathogens followed by *Bacteroids spp., Klebsiella spp.* and *Pseudomonas species.*[2,5] Cleaning of medical equipment, proper housekeeping and fumigation of neonatal units have some role in reducing the burden of hospital acquired infections.[6-11] Finding the sources of infection in one's own set up and eradicating the causative organisms is crucial for preventing morbidity and mortality. This study was designed to find out the potential sources of infection in our set-up and determine if fumigation with formalin solution and carbolic acid along with disinfection with Benzalkonium chloride solution mixed with dideacyldimethyl ammonium chloride and formic acid has a role in decreasing the culture positivity from environmental sources.

Methods
This was a cross sectional study conducted at the Neonatology Unit of the Children's hospital & the Institute of child health, Lahore during March 2007 - October 2012. We obtained samples for culture from the potential sources of infection like environmental air, suction bottle solution, liquid from oxygen flow meter bottle, patients' beds, incubators, warmers, nursing counters, hands of health care workers, intravenous stands, ventilators & its tubing's, suction machine & its tubing's, oxygen masks, ambo bags and laryngoscopes. We conducted fumigation/ disinfection after every four months and results of all of these conducted in study period was compiled together. Fumigation and disinfection was done according to hospital policy. Fumigation was done by formalin solution and carbolic acid after environmental cleaning. Cleaning of medical equipment was done with benzalkonium chloride solution mixed with dideacyldimethyl ammonium chloride and formic acid.

Floors, walls & windows of the ward were cleaned by phenyl floor cleaners. Samples were taken before and after doing the fumigation. Liquid samples were taken with dry swab technique while samples from semisolids & solid medium sources were taken with moistened swab technique.[2] Blood agar and MacConkey agar plates were placed in different units of the ward for 150-180 minutes to collect environmental air samples. These samples were used to inoculate blood and MacConkey agar plates in the laboratory and growth of microorganism was checked. The information in form of type and number and sites screened, organisms grown, and response to fumigation/disinfection was collected on a proforma and then entered and analyzed in SPSS16.0. Chi square test was applied to compare the sources of culture and fumigation, where number is less than five Fischer exact tests was used and paired t test was applied to find association between pre and post fumigation cultures. p-value < 0.05 was taken as significant.

Result

Total of 556 swab cultures were taken from different sources of neonatology unit. 288 samples were taken before doing fumigation and disinfection while 268 were taken after it. Samples for culture taken from NICU were 209, 223 from High Dependency Unit while 124 samples were taken from Special Care Unit. 456 samples were taken from semisolids and solid medium sources while 100 cultures were taken from liquid medium sources. Number of samples taken from different sources of the unit before and after disinfection and fumigation are shown in table 1.

Cultures were positive in 321 samples. In pre fumigation and disinfection 227 out of 288 cultures were positive while in post fumigation and disinfection only 94 isolates were detected from 268 cultures (p =0.02). All cultures taken from the environmental air before and after fumigation and disinfection were positive. Results of cultures from other sources were mentioned in table 2.

Most common microorganism detected from different sources is *Staphylococcus epidermidis* (n=96) followed by *Bacillus species* (n=67), *Klebsiella spp.*(n=59), *Staphylococcus aureus* (n=32), *Pseudomonas spp.* (n=29), fungi (n=6), E coli(n=4), *Acinetobacter spp.* (n=3), *Enterobacter* (n=2), *Serratia spp*. (n=2), *Burkholderia cepacia* (n=1) and *Micrococcus spp.* (n=1). Microorganism isolated most frequently from liquid sources was *Klebsiella* while from semisolid and solid sources is *Staphylococcus epidermidis*. *Staphylococcus epidermidis* is most frequently detected in environmental air samples, hands of health care workers, walls & windows of the ward and nursing counters. *Klebsiella* spp. was isolated from suction bottle solution & its tubings, ventilator tubings, ambu bags, oxygen masks and laryngoscope blade. *Pseudomonas spp.* was isolated from in oxygen flow meter bottle samples. *Bacillus spp.* is dominant in patients' beds, warmers, incubators, mother's beds and intravenous stands. Two cultures showed growth of *Serratia spp.*, one from suction machine and the other from laryngoscope blade, three cultures showed growth of *Acinetobacter spp.* and all were isolated from samples of ambo bags. Two samples one from laryngoscope blade and second one from suction machine showed *Enterobacter spp.* growth.

Table 1: Total number of samples taken from different environmental sources

Type Of Source	Sources	Pre fumigation	Post fumigation	Total
Air		32	32	64
Liquid	Oxygen flow meter bottle	28	26	54
	Sucker machine bottle	27	21	48
Solid	Suction machine tubings	9	8	17
	Patient Bed	20	20	40
	Ventilator tubings	9	11	20
	Walls/windows	32	29	61
	Nursing Counter	10	9	19
	Oxygen Mask	2	2	4
	Ambu Bags	25	25	50
	Warmers	22	23	45
	Laryngoscope Blade	29	24	53
	Incubators	27	26	53
	IV stand	3	3	6
	Hands of staff	5	--	5
	Mother Beds	9	10	19

Table 2: Comparison of cultures from different sources of Neonatology Unit before and after fumigation.

Sources	*Pre fumigation*		*Post fumigation*		*P value*
	Positive	*Negative*	*Positive*	*Negative*	
Environment	32(100%)	0	32(100%)	0	--
Sucker machine tubing	7(78%)	2(22%)	2(25%)	6(75%)	0.03
Suction machine bottles	26(96%)	1(4%)	6(29%)	15(71%)	<0.001
Patient Beds	19(95%)	1(5%)	7(35%)	13(65%)	<0.001
Ventilator tubing	6(68 %)	3(33%)	2(18%)	9(82%)	0.028
Walls/ Windows	21(66%)	11(34%)	5(17%)	24(83%)	<0.001
Nursing counters	7(70%)	3(30%)	2(22%)	7(78%)	0.037
Oxygen masks	1(50.0%)	1(50%)	1(50%)	1(50%)	--
Oxygen flow meter bottles	17(61%)	11(39%)	5(19%)	21(80%)	0.02
Ambu bags	19(76%)	6(24%)	4(16%)	21(84%)	0.001
Warmers	21(96%)	1(5%)	10(44%)	13(56%)	<0.001
Laryngoscope blades	20(69%)	9(31%)	2(8%)	22(92%)	<0.001
Incubators	15(55%)	12(44%)	9(35%)	17(65%)	0.12
IV stands	3(100%)	0	1(25%)	2(75%)	0.08
Hands of Staff	4(80%)	1(20%)	0	0	--
Mother Beds	9(100%)	0	6(40%)	4(40%)	0.33

Micrococcus spp was isolated from a sample from the incubator and one sample from a laryngoscope showed growth of *Burkholderia spp*.

Discussion

Environmental surfaces can become contaminated after exposure to colonized patients and these contaminated environmental surfaces of neonatal unit may be a risk factor for the acquisition of nosocomial pathogens by unaffected patients.[5]

Our study showed growth of microorganism from most of the hospital sources. Study done in India by Chandrashekar MR, *et al* in 1997 showed 84.8% swab samples from hospital environment indicated considerable infection.[4] Another study in Ghana by Newman MJ in 2002 showed 91% of swab culture taken from different sources of hospital environment yielded growth of pathogens.[2] V Rastogi in 2010 conducted a study in India that revealed that humidifier solution, water taps, hands of health care worker at neonatal intensive care unit are the sources of *Klebsiella Pneumoniae*.[12]

Study done by Newmann MJ in Ghana during 2002 showed that *Coagulase negative Staphylococcus* (44%) was the predominant microorganism in the NICU environment followed by *Bacillus spp.* (20%), *E coli* (12.5%), *Klebsiella spp.* (8.5%) and *pseudomonas spp*. (8.5%).[2] Study done in India by Chandrashekar MR, *et al* in 1997 showed that *Klebsiella spp.* (27.4%) as the predominant organism followed by *E coli* (16.8) in neonatal intensive care unit.[4] Pattern of microorganisms' growth is similar in our study which can be due to low resource set up in these countries.

We used environmental cleaning and fumigation to reduce the burden of pathogens and our results showed that these procedures are effective in reducing the number of bacterial isolates significantly. Similar results are in accordance of our results. Study done by Denton M with his colleagues in 2005 in UK showed that new cleaning protocols and use of 1000ppm hypochlorite solution reduced the number of bacterial isolates during an effort to control the outbreak of *Acinetobacter spp*. in a neurosurgical intensive care unit.[7] For improvement of the infection control Christine Roque in 2010 had evaluated the effect of dry mist hydrogen peroxide automatic disinfection device (Sterinis) which suggested that a rigorous control procedure including adapted cleaning and surface disinfecting protocol leads to rapid control of vancomycin resistant *Enterococci* transmission in hospital.[6] Barbut with his colleagues in 2009 compared the efficacy of hydrogen per oxide dry mist disinfection system and sodium hypochlorite solution for eradication of *Clostridium difficile* spores and proved that hydrogen peroxide dry mist disinfection system is more effective and might represent a new alternative for disinfecting the rooms of patients with *Clostridium difficile* infections.[8]

Our study showed that fumigation with formalin is ineffective to disinfect the environmental air. All samples taken from air after fumigation showed presence of pathogenic microorganisms. This may be lack of air filters in the air conditioning ducts of

the unit. Incorporation of the air filters and use of newer agents for fumigation may reduce the burden of pathogenic microorganism.

In our study *Staphylococcus epidermidis* was frequently isolated from environmental air samples, hands of health care workers, walls & windows of the ward and nursing counters. *Klebsiella spp*. was a common isolate in the suction bottle solution & its tubings, ventilator tubings, ambu bags, oxygen masks and laryngoscope blade. *Pseudomonas spp*. was found in oxygen flow meter bottle samples.

Many studies have documented the contamination of sinks and sink drains by *P. aeruginosa*. *Acinetobacter baumanii* has been isolated throughout the inanimate environment on the beds of colonized patients and on nearby surfaces (e.g., on mattresses and bedside equipment), in hospital rooms (e.g., on floors, sinks, countertops, and door handles), and in room humidifiers. *Clostridium difficile* commonly affects surfaces and equipment like commodes, bedpans, blood pressure cuffs, walls, floors, washbasins, and furniture. Environmental sites with Vancomycin resistant *Enterococci* involvement have included the gowns worn by patients and health care workers, medical equipment, microsphere beds, and environmental surfaces.[13-18]

There are multiple limitations of this study. Firstly, we collected cultures within few hours of disinfection and we cannot comment on the duration of the effectiveness of fumigation. Recontamination with pathogens is known to occur as soon as patients are readmitted and optimal frequency of the procedure has not been established. Secondly, *Staphylococcus epidermidis* is part of the normal flora of skin and significance of detection from the hands of HCW cannot be commented upon. Further, we did the fumigation and disinfection simultaneously and it is difficult to comment on their individual effectiveness

Conclusion

Pathogenic microorganisms were isolated from various sources of neonatal ward and are potential reservoirs for nosocomial infections. Environmental disinfection along with fumigation is effective in reducing the burden of pathogenic microorganisms. However we didn't find fumigation as a successful tool for disinfecting the environmental air.

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ORIGINAL ARTICLE

Culture Positive Meningitis in Cancer Patients; An Eleven-year Experience

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Abstract

Objective
To analyze the clinical presentation, microbiological spectrum and outcome of cancer patients with culture proven meningitis.

Methods
We retrospectively reviewed the data (2002-2012) of patients with various malignancies having the diagnosis of meningitis with positive microbiologic cultures of cerebrospinal fluid (CSF).

Results
We found 24 patients with meningitis and positive CSF cultures out of 80,000 cancer patients registered during the study period. The mean age at diagnosis of meningitis was 29.2 (Range 4-64) years. Fever was the most common presentation (87.5%) followed by headache (54.2%). Hematological malignancies comprised 41.6 % of the patients followed by CNS malignancies (20.8%). Three patients had profound neutropenia at the time of diagnosis. Gram stain of CSF was positive in 66.6%. The mean value of CSF proteins was 137.94 mg/dl and CSF glucose was 68.6mg/dl. *Acinetobacter baumanii* and *Staphylococcus epidermidis* were the most common organisms at 16.6% each (4/24), followed by *Streptococcus pneumoniae* (12.5%), *Listeria monocytogenes* (8.3%), methicillin resistant *Staphylococcus aureus* (8.3%), *Pseudomonas aeruginosa* (8.3%) and *Cryptococcus neoformans* (8.3%). Concomitant blood cultures were positive in 37.5% of the patients. Seventeen out of twenty four patients (70.8%) were alive by the end of treatment for meningitis while seven (29.2%) died.

Conclusion
Microbiologic etiology of meningitis is diverse in cancer patients and fever is the most common presenting symptom.

Key words
Meningitis, Cancer

Introduction

The immunocompromised state is an important host factor that can predispose to meningitis.[1] Cancer patients are predisposed due to the disease itself, immunosuppressive therapy, indwelling catheters and neurosurgical procedures.[2,3] The clinical presentation of meningitis in cancer patients may also differ as compared to immunocompetent patients who typically demonstrate fever, headache, vomiting and/or altered sensorium. In addition, the etiology of meningitis differs from that in the general community with more unusual and opportunistic pathogens.[4]

Pakistan, with a total population of 180 million people, has few cancer treatment facilities although cancer rates have been steadily increasing. Moreover, physicians specialized in Infectious Diseases are scarce in most of these centers despite high infectious complication rates due to delay in diagnosis, lack of knowledge and expertise.[5] Therefore it is important to characterize meningitis in cancer patients in a developing country and raise awareness. We aim to delineate the clinico-demographic features, CSF microbiology and discharge disposition in patients with meningitis in a cancer hospital in Pakistan.

Material and Methods

Study Setting
We retrospectively performed this study in the department Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC), Lahore Pakistan. SKMCH&RC is a 150-bedded institute and caters to patients from all over the country as well as from Afghanistan.

Patient selection
All cancer patients who had a positive CSF culture for bacterial, mycobacterial or fungal organisms in a compatible clinical setting irrespective of age from January 1st 2002 until December 31st 2012 were included. Viral meningitis was not recorded due to non-availability of diagnostics.

Exclusion criteria
Patients were excluded if their CSF cultures were negative despite clinical meningitis and abnormal CSF findings. Patients without CSF studies despite managed as meningitis were also excluded.

Profound neutropenia was defined as an absolute neutrophil count of less than or equal to 100 cells/mm.[3,6]

Data collection
Data was retrieved from the electronic database and patient

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records after coding for meningitis and CSF cultures. Data regarding age, gender, clinical signs on presentation, underlying malignancy, absolute neutrophil count (ANC), pathogen identified and outcome in terms of discharged, cured of meningitis or death due to meningitis were recorded.

Statistical analysis

Descriptive statistics were analyzed using SPSS 19.

Results

We identified 24 patients with meningitis and positive CSF cultures out of 80,000 patients registered and treated during the eleven-year period (2002-2012). Half of the patients developed meningitis during hospitalization, while half presented to the emergency department with meningitis, all of whom were on regular follow up with a preceding visit within the last 3 months, except three patients. The mean age at diagnosis of meningitis was 29.2 (4-64) years. We identified fever as the most common presentation 21/24 (87.5%) followed by headache in 13 (54.2%). Vomiting, signs of meningeal irritation fit and altered mental statuses were reported in 10 (41.7%) patients each (Figure 1). Hematological malignancies comprised 41.6 % followed by CNS malignancies in 20.8%. Lymphoma was the most common malignancy in 29% followed by carcinoma breast in 12.5%. Three patients had profound neutropenia at the time of diagnosis. CSF findings are given in table 1.

Staphylococcus epidermidis and *Acinetobacter baumanii* were the most common pathogens isolated. The list of the organisms isolated is shown in Figure 2. Concomitant blood cultures were positive in 37.5% of the patients. In two cases each of *Listeria monocytogenes* and *Cryptococcus neoformans*, and in two of three cases of *Streptococcus pneumonia*, both blood and CSF were positive. Seventeen out of 24 (70.8%) patients were alive by the end of management of meningitis while seven (29.2%) died.

Discussion

Over an eleven-year span, only a few cancer patients with culture proven meningitis were identified. Patients may have been missed because they were on antibiotics which inhibited CSF microbial growth, or a CSF study was deferred due to patient condition. We do not have any local data but studies from Thailand demonstrate that the yield of CSF cultures is significantly lower in nosocomial meningitis compared to community acquired meningitis (17.7% vs. 45.7%, p=0.006).[8]

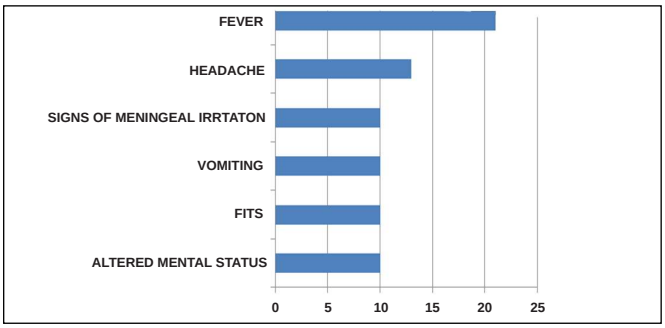

Fig 1. Presenting Signs and Symptoms in 24 cancer patients with culture proven meningitis.

Table 1: CSF Characteristics of cancer patients with meningitis

CSF characteristics	n =24
Appearance	
Clear	12 (50%)
Hazy/turbid	7 (29.1%)
Blood stained	5 (20.9%)
Clear Supernatant	20 (83.3%)
Gram stain	
GPC (Gram Positive Cocci)	11 (45.8%)
GPB (Gram Positive Bacilli)	2 (8.4%)
GNB (Gram Negative Bacilli)	1 (4.2%)
GNB+GPC	1 (4.2%)
Candida	1 (4.2%)
No organism seen	8 (33.3%)
CSF WBC (mean)/mm^3	179 (0-1881)
CSF Glucose (mean) mg/dl	68.6 (1-573)
CSF Proteins (mean) mg/dl	137.94 (2-839)

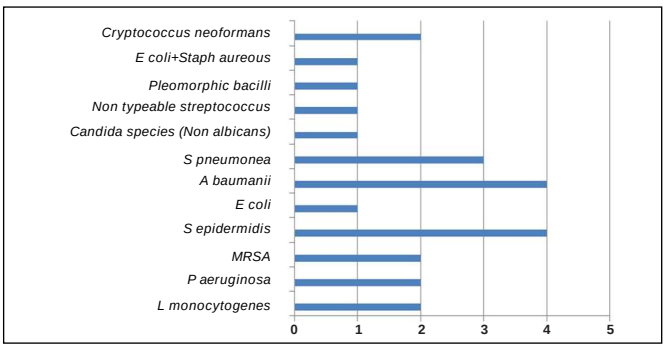

Fig 2. Pathogens cultured from CSF in 24 cancer patients with culture proven meningitis.

Mean age at diagnosis of meningitis was 29.2 (4-64) years; this wide range is because we included all patients with cancer and meningitis irrespective of their age group. Extremes of age is an additional risk factor for meningitis along with cancer as seen in our study with 37% of the patients less than 10 years of age and 8.3% above 60. This is not comparable with meningitis in the general population due to the highly selected population in our study.

The clinical presentation of meningitis in cancer patients may differ from immunocompetent patients. The classic presentation of meningitis (fever, headache and neck stiffness) was present

in 41% of our patients, similar to 44% reported in community acquired bacterial meningitis patients[1] but considerably higher than the study done in cancer patients by Safdieh and colleagues[7] where the triad was present in only 8% patients. In our study, 54% of the patients had at least two symptoms out of fever, headache, vomiting, neck stiffness, fits and altered mental status, in comparison to 95% in the general population.[1] Fever was the most common symptom (87.5%) in our patients, headache was present in 54.2% and signs of meningeal irritation were present in 41.7% while fever, headache and signs of meningeal irritation were present in 56%, 47% and 14% respectively in a comparable study by Safdieh and colleagues in cancer patients.[7] Signs of meningeal irritation, although classic for meningitis, are found in about 30% of community acquired meningitis.[9]

We identified a positive gram stain of CSF in 66.6% of the patients as compared to 60-90% in community acquired bacterial meningitis suggesting that the sensitivity of CSF gram stain in meningitis is lower in cancer patients.[1,10] Most of the positive gram stains were of Gram positive cocci (GPCs) (45.8%). This is comparable to prior study results conducted by Safdieh and colleagues where GPCs were most commonly (58%) seen on gram staining. Gram stain results guide choice of antimicrobials. In case of a negative gram stain, the empiric regimen is based on the specific age group and risk factors.[11]

CSF glucose levels was less than 40 mg/dl in 41.6% of our patients, low glucose was found in 71% in other study done in cancer patients and 50-60% of the bacterial meningitis in otherwise normal population.[7,8] Fourteen of 24 (58.3%) patients had raised CSF proteins (>40mg/dl) in our study as compared with forty nine of 69 (71%) in the study done by Safdieh and colleagues.[7]

CSF WBC count ranged from 0-1881 with a mean value of 179 cells/mm^3 in our study. This is comparatively a lower count than the usual count in otherwise immunocompetent patients (mean 4,442±216 cells/mm3)[8], and this could be explained on the low base line white blood cell count of our patients that ranged from 0-23,000 cells/mm^3 (mean 7501cells/mm^3). We found only three patients with profound neutropenia (absolute neutrophil count of <100 cells) and possible explanations for this low number could be, CSF analysis was not done due to the very low platelet count or use of empiric antibiotics which is a common practice in patients with febrile neutropenia. This is also confirmed in another study done in cancer patients with meningitis in which the mean WBC count was found even lower than our i-e 74 cells/mm^3. They identified six patients who had profound neutropenia and three of these neutropenic patients had a normal CSF[7] suggesting that a normal CSF cell counts may not be reliable in excluding meningitis in this group .

The majority of organisms isolated in our study represented nosocomial pathogens, most likely due to repeated exposure to hospital flora and having the additional risk factors of invasive procedures and immunosuppression. Pneumococcus was the third most common pathogen isolated and although it is not considered a nosocomial pathogen, invasive pneumococcal infection is more likely to occur in the immunocompromised host. Four of our patients had a neurosurgical procedure done during their course of cancer therapy prior to meningitis and the organisms isolated were Methicillin resistant *S aureus, S epidermidis, S pneumoniae and A baumanii,* two had an indwelling ventricular catheter in place. *L monocytogenes* were isolated in two of our patients, which is one of the most anticipated organisms in the immunocompromised population for which patients receive empiric cover. However, as shown in the study done by Safdieh and colleagues the frequency of *L monocytogenes* is decreasing compared to prior studies done at the same center (2 vs 27).[7]

Fungal isolates identified in our patients included candida non-albicans in one and *C neoformans* in two patients, all of whom had leukemia. Two of these leukemic patients had profound neutropenia at the time of diagnosis of meningitis. Tuberculous meningitis is a frequently reported problem in our part of the world[12] however in our study no mycobacteria were reported in the CSF in the last 11 years, CSF cultures for mycobacteria is routinely checked in our patients who have a compatible history or clinical suspicion of tuberculosis.

Mortality in our patients was higher than the study done by Safdieh and colleagues and that could be attributed to the differences in the type of cancers and the microbiologic etiology as elaborated in table 2. Mortality analyses done in the general population are greatly dependent on the etiology and the age of the patients and have a linear relationship with age.[1,7]

Limitations of our study are that it is a retrospective analysis and confounding variables cannot be controlled. Only culture proven meningitis patients were included in the study and all culture negative patients with meningitis and those who were treated for meningitis on clinical grounds without a CSF study were excluded therefore most likely understating the incidence of meningitis in cancer patients at our institution.

Conclusions

Microbiological etiology is diverse in cancer patients with meningitis and is mostly nosocomial in origin. Fungal meningitis is more often seen in patients with leukemia. CSF white cell count may not be as high as expected in bacterial meningitis especially in-patient who have low white blood cell counts due to chemotherapy and need large scale studies to explore this further.

Author's contributions

AM conceived the idea, participated in the design and drafting manuscript, FS supervised the whole process and critical review, AR contributed to the discussion and review, SAR contributed

Table 2: Comparison of present study with study done by Safdieh and colleagues of meningitis in cancer patients

	Present study (n= 24)	Safdieh[7] (n= 79)
Age	4-64 (29.25)	3-76 (46)
Fever	87.5%	56%
Headache	54.2%	47%
Signs of meningeal irritation	41.7%	14%
Vomiting	41.7%	-
Fits	41.7%	10%
Altered mental state	41.7%	35%
Hematologic Malignancies	41.6%	36%
Solid organ malignancies	29.1%	27%
CNS and head and neck tumors	20.8%	38%
Prior neurosurgery	16.6%	78%
CSF WBC (mean)	179	74
GPC	45.8%	68%
GPB	8.4%	10%
GNB	4.2%	14%
GPC+GNB	4.2%	
Fungi	4.2%	8%
Mortality	29.2%	13%

in data retrieval, data entry and statistical analysis

Conflict of Interest Statement

The authors of this study declare no conflict of interest.

Acknowledgment

We are indebted to the hospital's information management systems for assistance in data retrieval.

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ORIGINAL ARTICLE

Vaccine-Induced anti-HBsAb Level in 1-5 Years Old Malnourished Children

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Abstract

Objective
Viral hepatitis B is a major worldwide health problem. Hepatitis B vaccine is 95% effective in preventing infection and its chronic consequences. Several factors can influence on serological response to Hepatitis B vaccine. Nutritional status is also one of the major influencing factors in serological response. We aim to determine the titer of Anti-HBsAb levels in malnourished children 1-5 years of age immunized with Hepatitis B as per EPI schedule.

Method
This cross sectional study was conducted in the department of Paediatrics, King Edward Medical University/ Mayo Hospital, Lahore from January to June 2013. Hundred children, with a history of three doses of HBV vaccine, aged 1-5 years were selected consecutively. Nutritional status was classified on the basis of World Health Organization's Z-score (weight for age). One milliliter of venous blood was taken and anti-HBsAb was tested by enzyme linked Immunosorbant assay (ELISA). A cut off of ≥10 mIU/mL was considered as protective immune response. Data was analyzed using the SPSS 17.

Results
Mean age of the subjects was 23±5 months. There was male predominance (70%). Among total, 37% cases were severely malnourished. Over all seroprotection in malnourished children was 55%. There was not statistically significant difference in serological response amongst the groups according to their nutritional status.

Conclusion
Malnutrition has no effect on serological response of Hepatitis B vaccination in children 1-5 years of age.

Key words
Hepatitis B Vaccination, Children, Malnutrition

Introduction

Viral hepatitis B is a major health problem worldwide. It is estimated that 400 million people suffer from chronic hepatitis.[1] Seroprevalence of Hepatitis HBsAg in Pakistan is 2.4% while in Paediatric population under 5 year is 1.3% (0.9-1.6%).[2] Hepatitis B vaccine is 95% effective in preventing infection and its chronic consequences.[3] Several factors like type of vaccine, site, type and dose of injection, cold chain, race, genetic, immunity, and age at which vaccination administered can influence serological response to Hepatitis B vaccine.[1] Nutritional status is one of the major influencing factor in serological response.[4] Protein energy malnutrition (PEM) causes cellular and humoral immunity and phagocyte function disorders and decrease in production of complement level (except C4), secretary IgA, and cytokine production.[5]

Studies have evaluated the protective serological response of Hepatitis B vaccine in malnourished children but data is contraversial.[6,7] Furthermore, there is limited data from our population regarding serological response of Hepatitis B vaccine in malnourished children. Therefore, we aim to determine the serological response (Anti-HBsAb levels) in malnourished children 1-5 years of age who were vaccinated for 3-dose Hepatitis B vaccination in EPI (Expanded program of immunization) schedule.

Methods

This cross sectional study was conducted in the department of Paediatrics, King Edward Medical University/ Mayo Hospital, Lahore from January to June 2013. Informed consent was obtained from parents before enrolment. A total of 100 children of either sex between the ages of 1 and 5 years, who had received 3 doses of hepatitis B vaccines in EPI schedule, were enrolled by consecutive sampling through outpatient department. Vaccination status was confirmed from vaccination card. (By using WHO Health calculator, 100 children were required by using expected seroprotection of 95% children after 3-dose Hepatitis B vaccination schedule[8] at 95% confidence interval, 5% level of significance and 5% margin of error). The data was collected for name, age, sex, residence, Hepatitis B vaccination and nutritional status. Nutritional status was defined on the basis of Z-score of weight for age. (Z-score at ≤-3 SD was taken as severe malnutrition, ≤ -2 SD as moderate while child with Z-score at ≤ -1SD was considered as mild malnutrition. Child with Z-score at median was considered as normal.). A non-heparinized 1cc venous blood sample was drawn by aseptic measures and sample was sent to Paediatric microbiology/immunology laboratory of Mayo Hospital, Lahore

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for antibodies to hepatitis B surface antibody (anti-HBsAb) by ELIZA. Anti-HBsAb of titers ≥10 mIU/mL was considered as protective serological response. [Serological response was categorized as low-responders (10–100mIU/ml), adequate responders (>100–1000mIU/ml), high-responders (>1000mIU/ml)]. Data was analyzed using the SPSS 17. Fischer Exact test was used to determine the relation between nutritional status and serological response. P value < 0.05 was considered statistically significant.

Results

Study population was 100 children 1-5 years of age with mean age of 23±5 months. There was male predominance (70%). (Figure I) Median serological response was 18.60 (Range 2.82-65.15). Among total, 37% cases were severely malnourished. Seroprotection in children with mild, moderate and severe malnutrition was 13%, 12% and 21% respectively. In severely malnourished group, almost 95% were none or low responder, while 96% and 90% children was none or low responder in moderate, and mild malnutrition respectively. Similarly, 82% normal children had none or low serological response. However, there was not statistically significant relationship between the groups (table 1).

Discussion

Our study indicates that in severely malnourished group, almost 95% were none or low responder. This is comparable with Karaglu *et al*,[9] reported 97% seroprotection in 1-3 years old children while Muhammad *et al*,[10] reported high protective serological response in mild malnutrition and low in severely malnourished group. In contrast, Karimi *et al*,[1] and Jafarzadeh *et al*,[6] from Iran who found 60% overall seroprotection. However, these researchers found no significant correlation between malnutrition and level of immunization. In contrary to these authors, Rey *et al*,[7] found that nutritional status was significantly correlated with the response to Hepatitis B vaccine. In our study, there was no statistically significant relation of severity of malnutrition and rate of seroprotection. These seemingly contradictory findings can be due to racial differences or non-apparent exposure to Hepatitis B in endemic areas. Bhaskaram *et al*,[11] concluded that response of malnourished children to live attenuated measles vaccine was safe and effective whereas Helfand *et al*,[12] found that malnourished children had a reduced response to measles vaccination. We may comment that malnutrition in children cannot prevent a competent serological response to Hepatitis B vaccine. Given the small sample size, conclusion based on the severity of malnutrition is not possible.

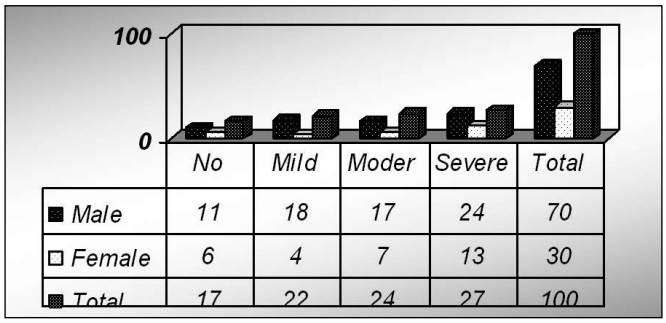

Fig 1. Gender distribution in relation to nutritional status

Authors believe that this is probably among the first reports of serological response to Hepatitis B vaccination in severely malnourished children. This study has limitation of small sample size as this size makes us impossible to conclude definitively about severity of malnutrition. This emphasizes on the necessity of more studies with the higher sample size and consideration of possible factors such as age, sex, and race, site of injection, nutritional status, vaccine brand, and calibration of kits.

Conclusion

The serological response to Hepatitis B vaccination in children 1-5 years of age is lower in malnourished children; however the difference is not significant.

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Table 1: Anti-HBsAb level in well-nourished and malnourished children

Age Group	Non-responders (<10 mIU/ml)	Low-responders (10–100 mIU/ml)	Adequate responders (>100–1000 mIU/ml)	Total	p value
No Malnutrition	08	06	03	17	
Mild Malnutrition	09	11	02	22	
Moderate Malnutrition	12	11	01	24	0.761
Severe Malnutrition	16	19	02	37	
Total	45	47	08	100	

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ORIGINAL ARTICLE

Practice and Knowledge of Infection Control Protocol among Dental Personnel

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Abstract

Background
To evaluate the practice and knowledge of infection control protocols among dental personnel of various institute of Islamabad.

Methods
A Cross sectional study was conducted among 340 participants 'which included dentists and clinical undergraduate students of Islamic International Dental College, Riphah University Islamabad and Margalla Institute of Health Sciences by a self-administered questionnaire. The dentists included senior faculty members, post graduate trainees, demonstrators and house officers. The data was analyzed using SPSS version 17.

Results
Out of 335 respondents 117(35%) gave history of needle injury and majority (n=261, 78%) practice single hand method for needle re-sheathing. Only 113(34%) respondents took a history of HIV and 134 (40%) were aware of proper glove use. Most (89%) of the participants had good knowledge regarding WHO hand washing protocol and 60%knew the proper way of using facemask. Nonetheless, knowledge of respondents regarding disinfection and sterilization, immunization and risk of transmission of HBV and HCV was inadequate.

Conclusion
The knowledge and practice of our participants regarding infection control protocol was satisfactory. However, the importance of infection control protocols should be further increased among the dental community.

Key Words
Infection control, HIV, Sterilization, Personal protective equipment

Introduction
Cross infection may be defined as the spread or transmission of an infectious and disease causing agent from one person to another, that can be a patient or an health care professional.[1,2] Effective infection control in the dental setup is a main concern as many diseases can be transmitted in dental environment. This occupational potential of spread of infection becomes more important with evidence of presence of various pathogens in oral secretions and that colonize oral cavity and respiratory tract especially mycobacterium tuberculosis and streptococci. There is also a concern of blood borne pathogens Hepatitis B, Hepatitis C and HIV (human immune deficiency virus).[3,4,5,6] During dental procedures, transmission of infections can be through direct contact with blood, saliva, contaminated treatment water from dental units, injury with an anesthetic needle or splash exposure of the mucous membranes, droplets and aerosols as well as indirect contact with contaminated instruments and surfaces. Similarly, poor compliance of dentist with infection control can jeopardize patient's health.[5, 6]

Studies have proved that in teaching institutions 20 to 38% of all procedures involved exposures to HIV, HBV and HCV.[7, 8, 9] Twenty reports have been published regarding transmission of hepatitis B from infected health care workers to their patients worldwide.[3, 10] There have been only two reports of transmission of HIV from infected health care workers to their patients, while that of Hepatitis C transmission from Health care worker to patient is reported to be very low.[3, 11]

Standard precautions are designed and integrated to protect health care professionals and patients from pathogens that can be spread by blood or by any other body fluid.[4, 5] However; infection control policies in developing countries have not been widely documented. Most hospitals have no infection control programs due to the lack of awareness of the problem or absence of properly trained personnel.[5]

Pakistan being a part of the developing world also lacks practice and implementation of infection control policies. There are many large and small dental practicing facilities which host patients who are not aware of the risks of un-protected dental procedures and others being aware, don't follow the recommended guide lines. The objective of our study is not only to assess the knowledge but also the practice of dentists.

Study Methods
This study was conducted at Islamic International Dental Hospital (IIDH); Riphah International University, and Margalla

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Institute of Health Sciences (MIHS), Pakistan in September 2012. This was a questionnaire based cross sectional study. The questionnaire comprised of 15 questions. Ten questions were designed to assess the participants' knowledge regarding infection control protocol. Each question had a score of one mark. The total marks for these ten questions were added up to obtain the knowledge score of the participants. Five questions were designed to assess the participants' infection control practice in the clinics. Each question had a score of one mark. The total marks for these five questions were added up to obtain the practice score for the participants. Non- probability quota sampling was used for the purpose of this study. All dentists working at IIDC and MIHS and third and fourth year undergraduate dental students at Islamic International Dental College and MIHS were also included in the study. To ensure confidentiality, each participant was assigned a unique code number. The data was analyzed using SPSS version 17.0. Frequencies and percentages were calculated for each question and were categorized for the students and dentists. Frequencies were also described for the knowledge and practice scores of the participants.

Results

A total of 340 participants were approached in the survey, 335 gave the feedback with response rate of 98.5%. Majority (81%) of the respondents were females. The age ranged between 20-57 years with mean age of 24 ±5.6 years. 153 qualified dentists and 182 undergraduate dental students submitted the questionnaire.

The respondents were asked about their own practice regarding history taking for HIV, history of needle stick injury, method of needle re-sheathing etc., results of which are summarized in table 1 and 2. The participants were asked regarding their knowledge about personal protective equipment, awareness about sterilization and disinfection and disease transmission and immunization, the results are summarized in table 3.

Discussion

To our knowledge this is the first local study in which both the practice and the knowledge aspect of infection control in dental care along with special emphasis regarding attitude and practice of HIV history taking has been questioned. This study has highlighted the poor knowledge and infection control related to HIV in Pakistan particularly in the dental community. However, since this study was conducted in only two dental teaching institutes, the findings are not generalizable. Nonetheless, this can be taken as a pilot study and can provide us with the platform required for future studies.

The oral cavity is a host to a horde of disease causing micro-organisms and most of the dental practice intervenes the natural barriers increasing the possibility of disease transmission. Needle stick injuries (NSI) is most common [7,12] and usually occur during injecting local anesthesia or during recapping or disposal among which recapping is known to be most common cause.[12] One hand or scoop method is the most widely accepted method for needle recapping.[12]

In our study 22.3% doctors and 12.5% students reported to have positive history of NSI which is very low unlike other studies. Reports of 45% from Lahore and 23% among students in United Arab Emirates respectively.[7, 13] This can be correlated to their awareness and proper use of needle recapping methods. Among those subjects who reported to have NSI most of them made themselves tested for HBV and HCV as incidence of these blood borne pathogens are reported to be high in Pakistan.

Fears of occupational transmission of HIV may have a significant impact on infection control practices among health care workers including the dental practices. Largely portrayed as a country free of this menace, the situation changed in 2004 when Pakistan experienced its first full-fledged HIV outbreak, 97,400 cases of HIV/AIDS were estimated in 2009 and more than 6,000 cases were registered till 2010.[14,15] This rise in incidence with a huge number of unregistered HIV infected patients, was the reason for this survey, as to how often do they take a history of HIV and in case if they do not take the history for HIV, what is the reason behind it. The most predominant reasons for not taking HIV history are that the respondent feels that patients

Table 1: Practice and knowledge of needle injury and method of re-sheathing among dental personnel

Questions	Dentists	Students
Positive history of needle injury	75 (22.3%)	42 (12.5%)
Did you tested for HBV /HCV after needle injury?	61 (81.3%)	19 (45.2%)

Method of re-sheathing	Two hand method		One hand method		Puncture proof method	
	Dentist	*Students*	*Dentist*	*Students*	*Dentist*	*Students*
	13 (4%)	18 (5%)	122 (36%)	139 (41%)	17(5%)	16 (5%)

Table 2: Practice and knowledge of history taking for HIV among dental personnel

Questions	Always		When suspected		Never			
How often do you take HIV history?	Dentists	Students	Dentists	Students	Dentists		Students	
	60 (18%)	53 (15.8%)	50 (14.9%)	55 (16.4%)	43 (12.8%)		74 (22%)	
Reason for not taking HIV history?	NA		NA		Social stigma	Low incidence	Patient unaware of status	Patients hide status
					29 (24.7%)	17 (14.5%)	43 36.7%)	28 23.9%)

Table 3: Practice and knowledge of PPE, sterilization and immunization amongst dental personnel

Questions	Right Answers		
	Dentists	Students	Total
Change of gloves if the procedure is longer than 30 minutes?	63	71	134(40%)
WHO recommendation for hand washing	138	161	299 (89%)
The reason for wearing the colored surface of the face mask outside	96	105	201 (60%)
Most commonly used disinfectant	57	82	139 (42%)
Effective method of removal of biofilm from dental unit waterlines	111	124	235 (70%)
Most sensitive indicator for assessing quality of autoclaving cycle?	66	43	109 (33%)
How often should sterilization cycle be verified through biological indicators?	23	57	80 (24%)
Frequency of changing plastic barriers from dental units and accessories?	129	151	280 (84%)
Risk of transmission in HBV or HCV	55	78	133 (40%)
Effectiveness of immunization of doctors	34	23	57(17%)

themselves are not aware of their HIV status and secondly HIV infection is still a matter of social stigma in a Muslim society of Pakistan.

The part ''B'' knowledge section was broadly divided into sections regarding a) personal protection equipment (PPE), b) sterilization disinfection and c) immunization.

Gloves are disposable items in particular and should always be changed when torn or perforated and also between patients.[16] Gloves acquire defects depending on glove type and procedure performed, in 30 minutes -3 hours' time, and thus should be changed.[17-, 19]

Hand hygiene is believed to be of utmost significance for lowering the potential of infective transmission to patients and HCP.[16, 20] The knowledge of participants regarding the WHO protocol of hand washing was excellent as 90% respondents knew that it is recommended to wash hands both before glove placement and after glove removal.

Apart from gloves, face mask is an essential component of PPE which safeguards against potential threat of infective micro-organisms produced by splash of saliva or blood. Existing data show infectious droplet nuclei measure 1–5µm; therefore, surgical masks used in healthcare settings should be able to proficiently filter the smallest particles in this range.[16, 23] Two thirds of the participants knew the reason for wearing colored surface outside while the rest were just practicing it as such following their colleagues.

In health-care facilities, items usually are disinfected by liquid chemicals or wet pasteurization.[24] The most commonly used high level disinfectant in dentistry is 2% gluteraldehyde followed

by per acetic acid, 60-70% ethanol etc. Only 40% of the respondents knew that aldehyde based disinfectants are commonly used in dentistry.[16,24]

Of all the current techniques available for sterilization, moist heat in the form of saturated steam under pressure is the most accepted method used. To ensure proper sterilization, monitoring of sterilization process is also mandatory.[24,25] Among three ways of monitoring "Biological indicator (BI)" is the most accepted method for monitoring the sterilization.[25] Only 32% knew that spore strip test is the most effective indicator for monitoring sterilization efficacy which depict their weak knowledge.

Another important source of pathogens that can transmit infection are the ''Biofilms'' which are microbial colonies that are firmly bound to surfaces and cannot be easily removed, and their presence is supported by unique structure of dental unit.[27] The participants of this survey demonstrated good level of knowledge about the effective method of biofilm removal from dental unit waterlines as 70 % responded correctly.

Clinical contact surfaces can become contaminated from patient materials either by direct spray or splash produced during dental procedures or by contact with gloved hands. These surfaces should therefore be covered with barriers impervious to moisture like plastic wraps, bags, sheets, or tubings and should be changed after every patient. Majority of respondents in our study have the correct knowledge regarding this.[20]

HBV has demonstrated the ability to survive and remain infectious in dried blood at room temperature on environmental surfaces for at least 1 week and probably longer.[30,31] HBV infected blood and blood products are more dangerous and can transmit infections in as little as 0.0000001 ml fluid, particularly when containing e antigen.[31,32] Relatively little is known about the occupational risk of HCV infection. The average transmission rate of HCV after exposure is about 1-2% which is much lower than HBV which is reported to be 22-31%.[30,33] Majority of respondents in our study have wrong perception about risk of transmission of HCV and HBV.

Vaccination against multiple diseases are recommended by the Advisory Committee on Immunization Practices (ACIP) for every health care personnel.[20,34] But some blood borne pathogens like HCV and HIV being threat in our society have no vaccines available,[20] therefore proper infection control protocols should be followed by doctors to save themselves and their patients. Majority of respondents in our study were not aware of the fact that immunization may help them protect against multiple diseases.

Conclusion

The knowledge and practice of infection control protocols demonstrated by the respondents of this study is generally satisfactory, nonetheless it is recommended to arrange separate course, workshops or seminars regarding infection control in order to improve the knowledge of the respective topic.

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CASE REPORT

An Unusual Case of Peri-Orbital Cellulitis

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Abstract

Orbital and Peri-orbital cellulitis (POC) is a potentially dangerous entity and medical emergencies rendering various diagnostic and therapeutic difficulties due to the many possible etiologies. Aside from sinusitis, the most important etiologies to pursue are lacrimal system infections and tumors. In cases presenting with non-specific clinical signs and symptoms, thorough etiologic work-up is essential, in view of the potential life-threatening, functional and social implications.Despite significant advances in antimicrobial therapies and diagnostic technologies, the management of POC often remains challenging, and rapid diagnosis and prompt initiation of therapy are important in minimizing complications and optimizing outcomes. We are presenting a case of POC with unusual presentation and unknown etiology.

Introduction

Peri-orbital cellulitis (POC) describes infections that involve the tissues posterior to the orbital septum, including the fat and muscle within the bony orbit. Peri-orbital cellulitis may be associated with significant complications, and as such, prompt diagnosis and expeditious treatment are lifesaving.[1-3]

Orbital cellulitis is usually a complication of paranasal sinus infection particularly in children. This is usually followed few to several days following upper respiratory tract infections in children.[4] Throughout the world, Peri-orbital cellulitis occurs more often in winter months because of its close associationwith upper respiratory tract infections. Most cases have a unilateral presentation.[5,6] In a retrospective analysis of pediatric orbital infections,the average age of affected patients was 6.8years, ranging from 1 week to 16 years.[7]

Rhino sinusitis, especially ethmoiditis, is by far the most common predisposing factor for pediatric Peri-orbital cellulitis. Peri-orbital cellulitis also can result from extension of external ocular infection such as a hordeolum or dacryocystitis/dacryoadenitis (infection of the lacrimal system); a dental abscess; a superficial break in the skin, or direct penetrating injury to the orbit; and hematogenous seeding.[8] Either the infection may dissect under the periosteum and lead to subperiosteal abscess intraorbital abscess may be formed secondary to a progressive and localized cellulitis. Without appropriate treatment, orbital infection may lead to serious complications, even death.[9-11]

We present a rare and potentially dangerous case of Peri-orbital cellulitis with thrombocytopenia and splenomegaly in a 12-year-old girl. To our knowledge, there are no reported cases of similar presentation in both adult and pediatric population.

Case History

Our patient was a 14 years old well thriving girl, resident of Karachi, who presented to our emergency department with repeated history of fever and bilateral orbital swelling since 3 months. She came with one week history of high grade, intermittent fever documented up to 39-40^{0}C , with bilateral conjunctivitis, that rapidly progressed to periorbital edema bilaterally, more on right side, so much so that she was unable to open her right eye within 1-2 days. She has been seen by a general physician and started her on Ceftriaxone once a day for 2 days, but as there was no improvement in her symptoms, she was brought to our hospital for further care. There were no associated complains of headache, photophobia, seizures, sorethroat, otalgia, difficulty in breathing, night sweats, dysuria or any rash.

Three months prior to her current illness, she had high grade, intermittent fever and bilateral orbital swelling.These complains continued for 3-4 weeks during which period she was prescribed oral antibiotics (Co-amoxicillin and cefixime) along with antipyretics and oral steroids which were given for a total of 4 weeks by a general physician that lead to recovery; however no cause has been identified. Her previous laboratory work-up

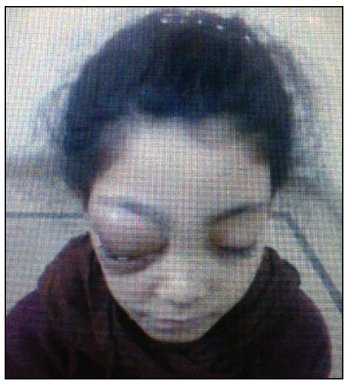

Fig 1. Showing marked swelling of right eye - Periorbital cellulitis. (This picture is published with due permission of patient and her family. Courtesy; Ali Faisal Saleem.)

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showed low hemoglobin of 7 gram/dl and low normal platelets of 80,000 /cmm^3. She has been transfused packed cells once. Her Chest x-ray, urine detailed reports were normal; while her abdominal sonography showed splenomegaly. She also had weight loss of 5 kg in last 3 months.

A couple of years back she had complains of left sided posterior auricular lymphadenopathy, initially small in size, gradually became bigger, later on also involved anterior and posterior cervical and submandibular lymph nodes on the same side, for which she took homeopathic treatment for 2 months after which lymph nodes disappeared.

She had also often been complaining of rhinitis, postnasal dripping and otalgia. At presentation, she was vitally stable; her weight fell on 10th percentile and height on 50th percentile. She had bilateral periorbital swelling, more on right side causing closure of the right eye with crusting, necrotic area over right upper eyelid. Right orbital swelling was warm, erythematous, tender to touch associated with pussy discharge. Right sided submandibular, anterior and posterior cervical lymph nodes were palpable, 1-2 cm in size, mobile, and non-tender, non-adherent. Spleen was palpable 4 cm below left subcostal margin. An initial impression of Peri-orbital cellulitis, possibly secondary to some hematological malignancy was made.

Her laboratory investigations showed hemoglobin of 8.7 g/dl, WBC of 4800 / cmm^3 with 68 % neutrophils, 24 % lymphocytes, and absolute neutrophil count was normal and platelets of 81/ cmm^3 were seen. Markers for tumor lysis were normal; LDH of 488 IU /L, calcium 8.4 mg/ dl, potassium 3.8 mmol/Phosphorus 2.7 mg/dl, uric acid 2.5 mg/dl. Liver and renal function tests were normal. Hepatitis B and C profile was unremarkable.Subsequent blood cultures showed no growth.

She was initially started empirically on Ceftriaxone and Clindamycin. Bone marrow biopsy was done to rule out bone marrow infiltrative disorder with granulocytic infiltration that could present like this.

Bone marrow biopsy was normal, blast cells were < 5 %. MRI head was done that was suggestive of diffuse pan sinusitis with post contrast enhancement extending in to the orbit, along the optic nerve route bilaterally, predominantly on right side. Enhancement was also seen involving the cavernous sinus, suggesting intracranial extension. Brain parenchyma was itself normal. Doppler ultrasound of abdomen was also done to rule out portal hypertension that showed splenomegaly of 15.4 cm with perigastric and splenic varices but no evidence of portal hypertension. Liver was seen to be slightly coarse in echo texture but normal size, having regular margins.

As MRI was suggestive of Peri-orbital, cellulitis possibly secondary to pan sinusitis, intravenous antibiotics changed to Meropenem and Vancomycin, central line was placed for prolong treatment with IV antibiotics up to 4 weeks and as she became afebrile, she was discharged. She was then readmitted after 3-4 days with fever.Due to severe hypersensitivity, reaction to Vancomycin it was switched to linezolid and Colistin was added due to sepsis. Gradually as her fever improved, she became hemodynamically stable and was discharged on intravenous Meropenem and oral Linezolid and plan was to givethese for a total duration of 4 weeks.

Discussion

Peri-orbital cellulitis is a serious infection of the orbit that involves the tissues posterior to the orbital septum and can result in significant complications, including visual loss, cavernous sinus thrombosis, meningitis, carotid occlusion, and intracranial abscess, thereby rendering this condition paramount in prompt diagnosis and management.[3,12]

There are several notable predisposing factors to the development of Peri-orbital cellulitis, including direct inoculation as a result of trauma or surgery, hematogenous spread in the setting of bacteremia, or extension of infection or inflammation from adjacent paranasal sinuses, ocular and adnexal structures.[13,14] The most frequent cause of Peri-orbital cellulitis is secondary extension of infection from the paranasal sinuses, particularly from the ethmoid sinus given the thin medial orbital wall.[9]

The bacteria most commonly implicated in pediatric Peri-orbital cellulitis include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, group A hemolytic *streptococci*, *Staphylococcus aureus*, other *streptococcal* species, and *anaerobes*.[12]

In culture positive pediatric Peri-orbital cellulitis, *S. aureus* and *Streptococci* species are the most commonly identified organisms.[7] In a more recent study examining the organisms isolated from cultures of orbital abscesses and sinus aspirates, *Staphylococcus* was the most common species (22 positive cultures, 36% of which were *methicillin resistant S. aureus*), followed by *Streptococcus*.[7] Non-spore forming anaerobic bacteria, including *Peptococcus*, *Peptostreptococcus*, and *bacteroides*, are less common causes and are associated with infections following human or animal bites.In immunocompromised patients, fungal etiologies of Peri-orbital cellulitis must be considered. *Mucormycosis* and *Aspergillosis* species are the typical causative fungal organisms.[2,15]

The management of patients with Peri-orbital cellulitis requires hospital admission and treatment with broad-spectrum antibiotics that have intracerebral penetration and anaerobic coverage, together with nasal decongestant treatments. Most patients respond to such medical therapy. However, small proportions of cases are complicated by the formation of an abscess, and require surgical drainage. Such cases require urgent treatment, due to the sight- and life-threatening nature of the condition.

Given the potential for significant complications, intravenous antibiotics are first line management.[2] Treatment regimens are based on empiric coverage of most common causative organisms, typically gram-positive organisms such as *Staphylococcus* and *Streptococcus*. In addition to the usual pathogens associated with acute sinusitis (i.e., *S. pneumoniae, H. influenzae,* and *M. catarrhalis*).[16,17]

Local trends in antimicrobial susceptibility are a critically important consideration. Methicillin resistance is commonly encountered in community-acquired infections in our institute, thereforeMRSA coverage should be strongly considered. Clindamycin plus a second- or third generation cephalosporin is a reasonable initial regimen. Vancomycin will provide coverage in the event the causative organism is MRSA or if *S. pneumoniae* is highly resistant to penicillin.When results of culture and susceptibility tests are available, antibiotic therapy may be adjusted if necessary. Intravenous therapy is maintained until the eye appears nearly normal. At that time, oral antibiotic therapy can be substituted to complete a 3-week course of treatment.[18,20]

Although vancomycin is the gold standard for MRSA infections, search for equally equally effective oral preparations with cost effectiveness have demonstrated the superiority of alternative agents such as linezolid and daptomycin.[21,22] Comparing the patients treated only with oral linezolid to the patients treated with i.v. vancomycin revealed no difference in outcomes despite the different routes of administration.[22] Therefore in our case with resolving cellulitis our patient was switched to oral linezolid along with meropenum.

Adjuvant therapies for rhino sinusitis, such as saline nasal irrigation, antihistamines, decongestants, mucolytic agents, and intranasal steroids, currently are not recommended.[23]

Conclusion

Peri-orbital cellulitis can have varied and difficult to diagnose presentation, also blood cultures may not be highly yielding. As in our case, based on the severity of infection the management was guided by empirical treatment with the prevalent notorious organisms. Due to long term management, antibiotics regimen should be governed by its efficacy and cost effectiveness

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Visual Impairment in Tuberculosis Meningitis

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Abstract

Visual impairment is one of the feared complications of Tuberculous Meningitis (TBM). The pathogenesis is diverse and may involve many factors including raised intra-cranial pressure, compression of optic chiasm and direct involvement of the optic nerve and may lead to blindness which is mostly irreversible. Here, we report three such cases with dimished vision of varying extent and history of fever; a 3 ½ year old boy with non-reactive, mid-dilated pupils, bilateral abducent nerve palsy and optic pathway dysfunction; a 15 year old girl with optic neuritis, diminished direct and consensual light reflexes, fixed, dilated pupils, and weak ocular movements; and a 14 years old boy with anisocoria, right occulomotor and left abducent nerve palsies, pale optic disc with visual acuity of 20/150 bilaterally. The patients responded well to ATT and supplemental steroids.

Introduction

Tuberculosis (TB) is the second greatest killer worldwide due to a single infectious agent. It is not only known for the mortality but also associated with a great number of devastating complications. Vision loss is one of the uncommon yet crippling complications of tuberculous meningitis (TBM) and can complicate up to 70% of the patients with TBM.[1-5] The causes of visual impairment may be secondary to optochiasmatic arachnoiditis and optochiasmaltuberculoma, third ventricular compression of optic chiasm, optic nerve granuloma, and ethambutol toxicity.[1,2] The presence of ophthalmoplegia and visual symptoms play a key role in predicting the prognosis and therefore assume a great significance.[1,6] We herein describe the clinical presentation and management of three Pakistani patients with visual impairment as a complication of TBM.

Case 1

A 3 ½ year old boy presented to paediatric infectious diseases clinic with fever and headache since 2 months. He also developed strabismus 1 month ago with associated vision loss since 15 days and increasing irritability for 2 days. The fever was high grade, continuous with vomiting. The parents denied presence of diarrhea, fits, altered behavior, dysuria, otalgia, joint pains, and difficulty in walking, swelling or rash. They had made multiple clinic visits and were prescribed antipyretics, analgesics and antibiotics and antimalarial with minimal relief in symptoms. The worsening pattern of the disease prompted a hospital referral where a thorough work up for pyrexia of un-known origin was done (table 1). The ocular complains were due to bilateral abducent nerve palsy and optic pathway dysfunction based on visual evoked potential (VEP) findings. A diagnosis of complicated meningitis was made and treatment was initiated. The patient was given intravenous (IV) ceftriaxone in meningitic doses, prednisone, paracetamol, vitamin B6 and valproic acid. The symptoms persisted despite the treatment so patient was referred to AKU. He was a febrile and vitally stable. The Glasgow Coma Scale (GCS) was 13/15 (E4 M6 V3) and there were no signs of meningeal irritation. His pupils were nonreactive and mid dilated and the optic disc was normal. The lack of response to previous medications, results of CSF analysis, visual changes and MRI findings of communicating hydrocephalus and meningeal enhancement of the basal cisterns suggested a diagnosis of TB meningitis. The patient was admitted and anti-tuberculous therapy (HRZ+Streptomycin) was started as per WHO guidelines with supplemental steroids and valproic acid. CT-head was done (table 1, figure 1) and because of massive hydrocephalus an external ventricular drain (EVD) was placed which was followed by a drastic improvement inirritability and GCS. On the third day of admission EVD was removed and ventriculoperitoneal (VP) shunt was placed. The child remained stable and was discharged.

Case 2

A 15 year old girl presented with high grade, intermittent fever

Table 1: Comparison of CSF Analysis of study patients

CSF Analysis	Case 1	Case 2	Case 3
Glucose	72	22	62
Protein	44	103	42
TLC	10	95	15
N/L	30/70	10/90	10/95
RBC	4	30	25
AFB Culture	negative	negative	negative
AFBPCR	negative	negative	negative

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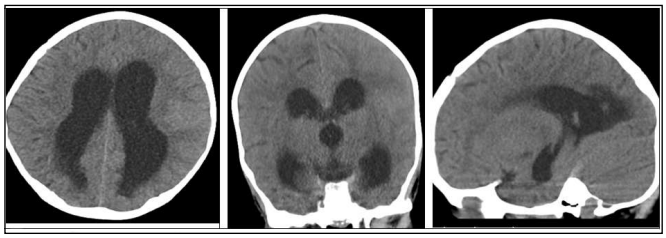

Fig 1: CT head showing evidence of hydrocephalus involving all the ventricles and diffuse cerebral edema in the left cerebral hemisphere close to the vertex with effacement of cortical sulci and gyri. The possibility of impending ischaemia in left cerebral hemisphere cannot be entirely excluded.

for 1 month, headache for 20 days, and loss of vision for 5 days. The parents reported some weight loss which was not documented. She received in-patient care for a week at a local hospital where she was treated with IV ceftriaxone and amox-clavulanic acid. Work-up including liver function tests, creatinine, electrolytes, typhi-dot, malarial parasite (MP), X-ray pelvis and abdominal ultrasound was normal. The patient had been prescribed ATT 3 months ago by her family physician but she did not adhere to the treatment and discontinued it within 2 weeks. She had a positive family history for TB and was not immunized. On examination, BCG vaccine scar was not seen. She was lean, lethargic and unable to stand without support but vitally stable. Her vision is limited to light perception and GCS was 15/15. Her motor and sensory neurological examinations were under normal parameters. Neck stiffness was present. Her pupils were dilated bilaterally and both direct and consensual light reflexes were sluggish. Ocular movements were weak. Ophthalmology examination was suggestive of optic neuritis. Based on the clinical findings, a provisional diagnosis of TB meningitis with optic neuritis was made. Appropriate laboratory investigations were carried out and the patient was admitted (table 2 and figur 2). Anti-TB treatment was initiated with intravenous dexamethasone, amikacin and levofloxacin. She developed tonic-clonic seizures on the first day of admission with altered mental status for which IV Levetiracetam was given. She responded well with resolution of fever, vomiting and improved GCS.

Case 3

14 years old boy resident of Sargodha has been treated as TBM at a local hospital due to complaints of fever, seizures and altered consciousness. Investigations are listed (table 1 and 2). He was treated with first line ATT (HRZ + streptomycin along with steroids) Because of evolving hydrocephalus and right sided ptosis he was referred to our hospital one month later. He was unimmunized and positive family history of tuberculosis (two elder sisters being treated for pulmonary TB 3 years back but sputum smear negative). On examination he was pale, emaciated child, vitally stable and a febrile. On eye examination there was an isocoria with right pupil was fixed and dilated. He was hypertonic with power of 3/5, deep tendon reflexes were brisk with negative Babinski's sign. Because of hydrocephalus on CT, an EVD was placed (figure 3) Ophthalmology examination showed right occulomotor and left abducent nerve palsies, pale optic disc with visual acuity of 20/150 both sides. VEP revealed relative integrity of optic pathway. After EVD placement the child improved dramatically and was discharged on ATT in stable condition.

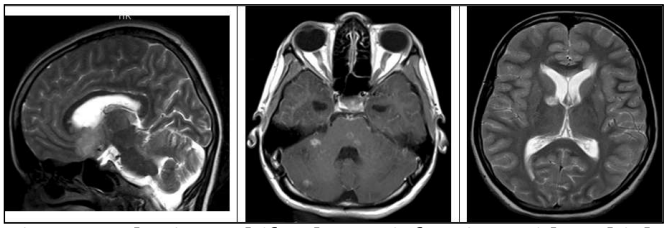

Fig 2: MRI brain: multifocal acute infarctions with multiple small tuberculomas within the brain parenchyma involving both supra and infratentorial compartments. These are associated with diffuse nodular enlargement more marked in basal region.

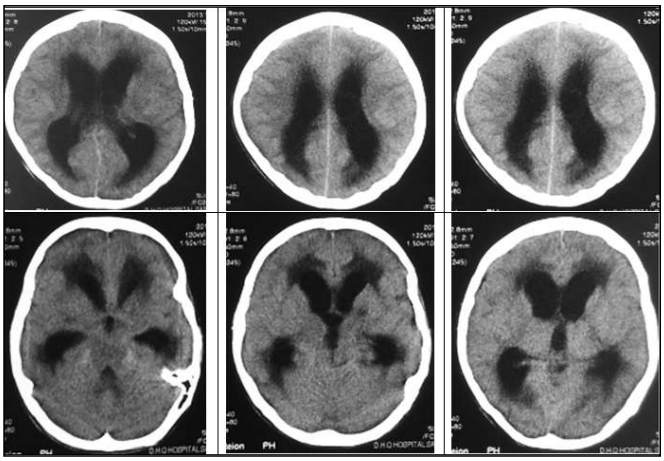

Fig 3: Ventricular dilatation and cerebral edema. Multiple hypo attenuating partly defined rounded area in basal ganglia and thalamus bilaterally.

Discussion

In this case series we report some of the cases with ocular complications of TBM. Our first patient had visual loss due to optic pathway dysfunction secondary to hydrocephalus induced ischemia and a squint due to abducent nerve palsy. Since all ventricles were dilated, there may have been compression of the optic chiasm by the third ventricle. MRI findings also showed hyper-intense signals along the periventricular region of occipital horns bilaterally which was suggestive of subependymal seepage and further increase in the pressure and ischemia. We did not observe optic disc swelling in our patient. We suspected optic neuritis in our second patient. She, however, had a normal VEP test whereas our third patient had occulomotor and abducent nerve palsies.

Blindness in TBM may revolve around number of basic pathophysiological processes including chronically raised intra

Table 2: Clinical and Radiological Features of patients before and after treatment with antituberculous therapy and steroids.

	Case 1	Case 2	Case 3
Age (years)	3.5 years	14 years	15 years
Gender	Male	Female	Male
Diagnosis of TBM	TBM with visual impairment	TBM with optic neuropathy and caudate lobe infarct	Complicated TBM with communicating hydrocephalus +cranial nerve palsies
Ophthalmological findings before treatment	Suggestive of optic neuritis VEP: bilateral optic pathway dysfunction	Suggestive of optic neuritis VEP: Normal	Suggestive of optic neuritis VEP : relative integrity of optic Visual field: Right: 79% Left : 95%
Ophthalmological findings after treatment	Lost to follow up	Lost to follow up	Lost to follow up
MRI findings before treatment	Moderate ventricular dilation of all ventricles suggestive of communicating hydrocephalus, slight meningeal enhancement of the cortical sulcus and basal cisterns:	Multifocal acute infarctions with multiple small tuberculomas within the brain parenchyma involving both supra and infratentorial compartments .These are associated with diffuse nodular enlargement more marked in basal region	Not done
CT findings before treatment	Showed evidence of hydrocephalus involving all the ventricles and diffuse cerebral edema in the left cerebral hemisphere close to the vertex with effacement of cortical sulci and gyri. The possibility of impending ischemia in left cerebral hemisphere cannot be entirely excluded	Redemonstration of multifocal established infarcts, mild hydrocephalus, infratentorialtuberculomas and diffuse, nodular leptomeningeal enhancement. No new abnormality identified.	Ventricular dilatation and cerebral edema. Multiple hypo attenuating partly defined rounded area in basal ganglia and thalamus bilaterally

NOTE: TBM, Tuberculosis Meningitis; CT, computed tomography; L, left, R, right; MRI, magnetic resonance imaging;

cranial pressure due to hydrocephalus and/or tuberculomas which may result in partial or complete optic atrophy; pressure related damage to optic nerve from constricting optochiasmicarachnoiditis (OCA); tuberculous optic neuritis; toxic optic neuritis from the use of ethambutol; infarction of the optic pathway and chiasm because of tuberculous endarteritis; or as a result of direct involvement of the optic pathways including the optic nerve and optic chiasm by basal arachnoiditis.[5, 7-13]

Lorber *et al* followed 100 patients with TBM for a period of 5 to 10 years and found 3 patients with complete loss of vision due to total optic atrophy.[5,14] Another study described some degree of loss of vision in 5.3% and complete visual loss in 8.6% of 374 children with tuberculous meningitis.[5] In a recent study from India, Sinha *et al* found visual impairment in one-fourth of patients with TBM and explained the various causes of loss of vision in the patients.[1] They suggested that the probable predictors of blindness in TBM include presence of papilledema, cranial nerve palsies (II, VI, VII), TBM stage II and III, raised CFS protein (>1g/L) and optochiasmaticarachnoiditis and optochiasmaltuberculoma.[1] In their study, optochiasmaticarachnoiditis (OCA) was found in 41% of the patients with visual changes and the second most common reason was optochiasmaltuberculoma, noticed in about 22% patients.[1] They reported only two patients who had vision loss

as a result of hydrocephalus and the consequent compression and ischemia of optic nerves.[1] Other have identified causes of vision impairment are papillitis, optic atrophy, occipital infarct, and ethambutol toxicity.[1,15-18]

Mooney first noticed the association of hydrocephalus with vision impairment.[1,15] Insertion of a ventriculoatrial shunt to lower the intracranial pressure and resulting ischemia significantly alters the disease progress and may result in improved levels of consciousness, resolution of hemiplegia and aphasia, and the return of vision in patients who have been blind for 4-6 weeks.[19]

The presence of optochiasmatic arachnoiditis (OCA), an abnormal thickening of the arachnoid in the region of the optic nerves and the optic chiasm, causes abnormal vision by exerting excessive pressure and traction on the nearby structures.[1,18,20] The loss of vision in OCA is often insidious and progresses gradually but in severe cases it can end in sudden blindness.[18] The sudden visual impairment may be due to decrease in blood supply or sometimes from a rare paradoxical reaction during the antitubercular treatment (ATT) period after stopping steroids.[18] The diagnosis of OCA is made on typical neuroimaging findings of perichiasmal enhancement and hypertrophy of chiasma and cisternal segment of optic nerves.[17,18,21] Hydrocephalus is a common finding in patients with OCA.[18] The prognosis in most of the TBM patients with OCA remains poor. Aaron *et al* in their study concluded that only 17% of the patients with established OCA showed improvement with ATT,[20] therefore, it is vital to maintain a low threshold to do a thorough ophthalmological evaluation in TBM patients presenting with any of the aforementioned predictors. They also emphasized that early detection is crucial because in 52% of the patients, the visual symptoms did not worsen once the treatment was initiated.[20] Treatment options from OCA include steroids, intrathecalhyaluronidase,[20,22] thalidomide,[20,23] and microsurgical intervention.[10,20]

Since TB is treatable and to a great extent preventable, it deserves international priority to increase the awareness about its possible complications and the need to manage these patients before any of the complications set in. The patients responded well to Anti TB treatment. Therefore it is necessary to identify vision impairment early in TBM and initiate treatment promptly especially in our country which ranks fifth on the list of countries with a high burden of TB worldwide, according to the world Health Organization (WHO) estimates.

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CASE REPORT

Aspergillus flavus Arthritis: A case report and review of literature

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Abstract

The incidence of invasive *Aspergillus* infections is on the rise due to frequent use of immunosuppressive modalities in patients with cancer and autoimmune disease. We report a case of *Aspergillus flavus* arthritis of the knee joint in a 51-year-old male who at the time of infection had recently been diagnosed with adenocarcinoma of the lung with brain metastasis. A diagnosis of *Aspergillus flavus* arthritis was based on aspiration and culture of the right knee joint fluid. The symptoms resolved with administration of Itraconazole. Thus it is important to consider fungal etiology in cases of arthritis in cancer patients.

Key words

Aspergillus flavus, Arthritis, Neoplasm

Introduction

Aspergillus is a pathogenic mold and includes more than 100 reported species, any of which can cause invasive disease. *Aspergillus fumigates* (*A. fumigatus*) accounts for most of the cases, followed by *Aspergillus flavus* (*A. flavus*). Invasive Aspergillosis mostly affects patients having immunocompromised status i.e., cancer and after transplant,[1] but cases have been reported due to decreased immunity as a result of corticosteroid treatment and use of antimicrobial agents disrupting the normal flora, or by a local point of entry.[2] Aspergillosis commonly involves the lungs, gastrointestinal tract, brains, kidneys and liver. Cases of primary aspergillosis in healthy individuals are rising,[3] however articular aspergillosis still remains infrequent. We are here describing an unusual case of articular aspergillosis in a patient who was recently diagnosed as adenocarcinoma of the lung and who at the time of infection was not overtly immunocompromised. We also review reported cases of articular aspergillosis of which only one was reportedly caused by *A.flavus*.[4]

Case report

A 51-year old male, smoker (30 pack years) presented to the hospital with a two month history of non-productive cough with increasing frequency of headaches and right sided body weakness, and a computerized tomography (CT) of the brain showing a 3 x 3 cm intra axial mass in the right temporal region. Further testing included: a full body CT scan which revealed a right sided lung lesion and ipsilateral small pulmonary nodules suggestive of a lung tumor; a magnetic resonance imaging (MRI) of the brain showed an enhancing mass in the right temporal lobe measuring 3.8 cm with extensive surrounding vasogenic edema and mass effect with contralateral midline shift. In keeping with the above findings bronchoscopy and tissue biopsy for lung mass (histopathology of which revealed it to be Adenocarcinoma and cultures of lung lesions were negative for any fungus or mycobacterium) and radiation therapy to brain were planned.

Five days after his initial presentation he presented to the emergency room with complaints of pain and weakness in his right lower limb radiating to the foot. Examination of the lower limb was unremarkable and he was discharged on oral analgesics. He presented two days later with unremitting pain of right knee with decreased joint mobility, an x-ray of the right knee joint revealed supra-patellar joint effusion but no bony or joint abnormality and he was discharged on pain control and Co-amoxiclav. On the following day he was seen in orthopedic clinic and found to have mild swelling of right knee, pain on movement with decreased range of motion. He was afebrile and laboratory investigations revealed an ESR of 87 mm, C-reactive protein of 186.6 and white blood cell count of 13,040/ul. His joint fluid was aspirated and sent for culture and sensitivity, and the patient was admitted and started on intravenous ceftriaxone. Culture of the joint aspirate grew *A. flavus* at 36 hours and itraconazole 200 mg bid was also started. The patient responded extremely well to the initial 4 weeks of treatment with itraconazole as on subsequent follow up visits in orthopedic and infectious disease clinics the knee swelling and pain had resolved and he had gained full range of motion of his knee. He is currently receiving chemotherapy for his lung cancer and being seen in follow up.

Discussion

Human Aspergillosis is an opportunistic infection encountered commonly in immunocompromised patients; however cases have been reported in otherwise healthy individuals.[5] Musculoskeletal aspergillosis is rare and retrospective analysis of literature revealed only a handful of reported cases (Table 1), with only one case other than ours that could conclusively be attributed to *A. flavus*.[4] The route of infection in our patient was unclear.

Many treatments have been instituted in the past with earlier

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Table 1: Review of cases with articular Aspergillosis[5]

Age / Sex	Comorbid conditions	Site of infection	Treatment	Outcome
18 y / Male	Acute Lymphoblastic Leukemia	Right shoulder	Voriconazole + Capsofungin	Resolved
83 y / Male	Osteoarthritis	Knee	Amputation + Voriconazole	Death
18 y / Male	None	Both knees, ankle MP joints	Itraconazole	Resolved
69 y/ Male	Vascular surgery	Knee	Amphotericin B and debridement	Resolved
51 y / Male	Cirrhosis	Knee	Itraconazole and debridement	Resolved
88 y / Male	Subacromial arthroscopic decompression and open rotator cuff repair	Right shoulder	Voriconazole and debridement	Resolved
34 y / Male	Renal transplant	left ankle	Amphotericin B and synovectomy	Resolved
67 y / Male	Right parotid epidermoid carcinoma post resection and irradiation therapy	Right TM joint	Amphotericin B and Debridement	Resolved
64 y / Male	Bilateral lung transplant	Right ankle	Poasaconazole	Resolved
29 y / Male	Renal transplant	Knee	Amphotericin B and Rifampin	Death
59 y / Male	Acute Lymphoblastic Leukemia	Right wrist	Itraconazole	Death

cases being treated with Amphotericin B, but best results of recovery are seen when combination treatments are used i.e. antifungals plus surgical intervention (Table 1), as surgery reduces fungal load and removes necrotic material. This increases the antibiotic penetration into the tissue.[6] Our patient had already undergone surgical debridement of his knee joint and cultures proved it to be *A. flavus* and our medical treatment of choice was itraconazole over Amphotericin B which has relatively poor bone penetration and more toxic profile making it a less attractive therapeutic option.[7] Even though voriconazole has been shown to be much more effective and better tolerated with higher joint penetration its availability and price limited its use in our setting. Our patient however recovered fully with Itraconazole and surgical debridement and went on to receive chemo and irradiation therapy for his cancer.

To conclude, it is important to consider fungal etiology in patients of monoarthritis and underlying malignancy even without other site of infection. Our case report showed that *A. flavus* arthritis responds well to Itraconazole and surgical intervention where availability and affordability of voriconazole is an issue.

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Antibiotic Stewardship Initiative in Pakistan (ASIP)

Statement from Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP)

The global challenge of antibiotic resistance is monumental with almost all countries and regions being affected including Pakistan.[1-5] Antibiotic misuse and overuse have contributed tremendously to this major health crisis. As an array of newer super bugs, such as carbapenem resistant *Klebsiellapneumoniae*, *ESBLs*, *NDM-1*,*MRSA* and *VRE*spread in healthcare and community settings alike the race to contain them has taken center stage at many forums. The reasons for this urgency are the increasing drug resistance in many healthcare settings with higher morbidity, mortality and costs.[6,7]

In Pakistan the antibiotic misuse is equally huge and tackling it will be an equally daunting and challenging task.[8]**Antimicrobial stewardship** is an emerging concept defined by a series of strategies and interventions aimed toward improving appropriate prescription of antibiotics in all healthcare settings.[9,10] The ultimate goal is the preservation of current and future antibiotics against the threat of antimicrobial resistance with improving patient safety and reducing healthcare costs.

Antibiotic stewardship is defined as "An ongoing effort to optimize antimicrobial use in order to improve patient outcomes, ensure cost effective therapy, and reduce adverse sequelae of antimicrobial use (including antimicrobial resistance)."[9,10] The major team members of Antimicrobial stewardship Programs (ASPs) are a *"Core members of a multidisciplinary antimicrobial stewardship team such as an infectious diseases physician and a clinical pharmacist with infectious diseases training, with the inclusion of a clinical microbiologist, an information system specialist, an infection control professional, and a hospital epidemiologist."* Two major strategies for antimicrobial stewardship currently endorsed include preauthorization/formulary restriction and prospective audit with feedback.[10]

ASPs have made major impact on infection rates, resistance patterns, costs and clinical outcomes in many studies.[11-13] Even in community settings it has proven to have impact.[14,] **Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP)** plans to address ASP at both institutional and community levels. These are increasing being employed in some developing countries.[16,17]

Given ASPs proven efficacy with major gains in many settings it is thus imperative that such initiatives and efforts be taken across Pakistan. MMIDSP is ardent to take the lead with involvement of major stakeholders from professional societies and policy makers of public and private institutions by launching "**Antibiotic Stewardship Initiative in Pakistan (ASIP)."** These include Pakistan's Medical Organizations, Medical Colleges and Postgraduate institutions, Provincial and Federal Health authorities and Non Governmental Organizations (NGOs) such as Drug Regulatory Authority of Pakistan (DRAP), Provincial Ministries of Health, professional bodies such as Pakistan Medical and Dental Council (PMDC), Pakistan Medical Research Council (PMRC), Pakistan Medical Association (PMA), Pakistan Pediatric Association (PPA), Pakistan Academy of Family Physicians PAFP), Pakistan Antimicrobial Resistance Network (PARN), *Pakistan Pharmaceutical* Manufacturers *Association (PPMA)*, Heart File *and* World Health Organization (WHO).

Aims of ASIP:

1. Acknowledge that there is an urgent need to initiate measures to tackle the growing hazards of antibiotic resistance and irrational use of antibiotics, and join international efforts to control this threat.
2. Encourage and implement initiatives to improve infection control standards in hospitals.
3. Include structured training in rational antibiotic usage and infection control in the medical curriculum at undergraduate and postgraduate levels.
4. Emphasize Continuing Medical Education (CME) in rational antibiotic usage and infection control for practicing doctors.
5. Standardize Microbiology laboratories in Pakistan. Hospitals must have good quality Microbiology laboratory or should be willing to outsource specimens, in the absence of a standardized laboratory.
6. Collaborate with Pakistan Medical Research Council to initiate surveillance of antimicrobial resistance at private and government hospitals and university labs.
7. Partner with EMRO/WHO to interact with the government on issues related to drug resistance, antibiotic policy, and infection control.
8. Liaise with professional organizations to initiate infection control and antibiotic stewardship awareness activities among the society members, utilizing the extensive network of local branches of all societies.
9. Participate with electronic and print mass media to raise public awareness on the dangers of misuse of antibiotics.
10. Evaluate the extent and to regulate the usage of antibiotics in veterinary practice.
11. Formulate and present a policy on rationalizing antibiotic usage in the country, both in hospitals and over the counter through collaboration with MMIDSP.
12. Formulate a national policy to control the rising trend of antimicrobial resistance, after consultation with all relevant stakeholders and then take all possible measures to implement the recommendations.

In conclusion ASPs have proven value in all healthcare systems and are an urgent need of the day in Pakistan. We all must come together to achieve in a long lasting and sustainable way. MMIDSP welcomes all to come and join hands on this platform to make it a success.

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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