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Chest X-ray: Left sided hydropneumothorax with collapsed left lung.

Courtesy: Syeda Sobya Owais, Shifa International Hospital, Islamabad
Human Papilloma Virus Vaccination and its Future in Pakistan; Are we ready yet?

Approximately 5% of all cancers worldwide are caused by HPV. In United States, 3% of all cancers in women and 2% among men are caused by HPV. A variety of malignancies and pre-malignancies are linked with HPV. HPV is associated with almost all of cervical cancers with HPV type 16 and 18 associated with 70% of all cases. HPV causes about 95% of anal cancers with HPV 16 accounting for most of them. About 70% of oropharyngeal cancers are caused by HPV. HPV is associated with various other cancers as well. In United States, it causes 65% of vaginal cancers, 50% of vulvar cancers and 35% of penile cancers with majority of them caused by HPV type 16.

The trend of Human Papilloma Virus led cancers are showing a rising trend in Pakistan. According to Cervical Cancer Global Crisis Card (CCGCC), Pakistan ranks seventh in terms of annual death count due to cervical cancer. Cervical cancer ranks as third leading cause of female cancer mortality in Pakistan.

HPV 6 and 11 are low risk viruses causing genital warts whereas HPV 16 and 18 are considered high risk accounting for 70% of cervical cancers. In developing countries, cancer treatment costs keep increasing with poor survival rates with patient burden borne by society at large. It is essential to identify a target age and population for screening and vaccination to have a significant impact; data suggests that by Quality adjusted life years (QALY) measurement, cost effective vaccination with maximum impact should happen in adolescent age.

Two vaccines, quadrivalent HPV vaccine Gardasil-4 and bivalent HPV vaccine Cervarix were developed. The former covers HPV types 6, 11, 16 and 18 while the latter covers HPV types 16 and 18. These vaccines are highly effective when administered before sexual activity. WHO recommends two doses of these vaccines spaced 6-12 months apart, for girls aged 9-13. Gavi-the Vaccine Alliance provides subsidies to introduce vaccinations in Low and Middle income countries.

According to a study in Lancet, to analyze cost effectiveness and health effects of vaccination program, a Microsoft Excel Based model called Pappiloma Rapid Interface for Modelling and Economics (PRIME) was established. The system accounted for vaccination effectiveness before sexual debut and correlated with cervical cancer burden and mortality. 179 country data with a vaccination cohort of 58 million adolescent females were studied. Using the PRIME model, it was determined vaccination prevented 690 000 new cases of cervical cancer and 420 000 deaths mostly in low and middle income countries at a cost of USD 4 billion. In 87% of the studied countries, every disability adjusted life year (DALY) averted costed less than the Gross Domestic Product (GDP) of the country, making the vaccination very cost effective. Pakistan is a GAVI supported country, however the absence of HPV vaccination program has kept the market price for vaccination high and out of reach for the majority population.

Safety and efficacy of HPV vaccinations have been demonstrated by many studies in the past. However, HPV vaccine has had concerns in Japan which led to its drop of vaccination coverage from 70 percent to just 1 percent. In spring of 2013, the media repeatedly reported pain and motor disability in girls receiving vaccination even though it is not evidently clear if these effects are caused by the vaccine. The Japanese Ministry of Health, Labour, and Welfare suspended its active recommendation for girls to receive HPV vaccinations in June, 2013 decreasing coverage significantly. According to a study in Lancet Oncology, Japanese women who became adolescent between 1993-2008 are at increased risk of developing cervical cancer. The calculated risk significantly increases each year with girls who became adolescents when vaccine was discontinued at a higher risk compared to girls who were adolescent when the vaccine was introduced.

As much as there is need for HPV vaccination, the question arises if we are ready as a society for a successful vaccination program. This dilemma could be understood from different perspectives. There is a difference between low and middle income countries and high income countries in terms of annual cervical cancer incidence and it would be unfair to label such a huge difference in numbers only due to preventive strategies. There is marked differences in educational levels, knowledge of cervical cancer, access and awareness. Also, there is deep rooted stigma associated with the disease which pose barriers to access.

Another way of understanding this problem is to look at another vaccination program involving similar age group and population. A study was conducted to access tetanus toxoid (TT) vaccine in women of childbearing age in Karachi due to high incidence of neonatal tetanus despite vaccination program introduction. Over 50% of women did not receive vaccination and non-vaccination predictors included young age without formal education, poor knowledge about disease process and complications, living with extended family, poor family support and other members of family making decisions related to women’s health.

It is very important to prevent HPV associated cancers especially in low and middle income countries where there is huge economic and social burden due to cancer morbidity and mortality on society. GAVI drew very important conclusions from their HPV demonstration projects and suggests School Based delivery works, grassroots communication, integration with routine immunization and delivery with other health programs. However, it is equally essential to understand local
parameters. One such example is school based delivery networks might not work in Pakistan since there is only 44% female enrollment in schools. Therefore, social and cultural dynamics and tailored supportive strategies are needed to engage communities to improve their knowledge, attitudes and practices. By doing that, we can achieve successful coverage of introduced vaccination HPV program.

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Background

Pakistan carries a high burden of chronic hepatitis and mortality due to hepatic failure and hepatocellular carcinomas. Keeping in view this potential threat all the Frontier Corps recruits are screened for the Hepatitis B surface antigen (HBsAg) and Hepatitis C virus antibodies (Anti-HCV) before induction.

Subjects and Methods

Sera of healthy adult individuals who presented for medical evaluation as pre-recruitment criteria in the Thall Scouts, Frontier Corps (FC), Khyber Pukhtunkhwa (KPK) were screened for HBsAg and Anti-HCV by rapid method. Positive cases were confirmed by Enzyme-linked immunosorbent assay (ELISA) technique from Combined Military Hospital (CMH), Peshawar.

Results

A total of 552 individuals were examined. Out of these, 12 (2.17%) individuals were HBsAg positive whereas 7 (1.26%) were positive for anti-HCV. None of the recruits was positive for both HBsAg and Anti-HCV.

Conclusion

This study which evaluated predominantly healthy young male population at KPK, showed a high seroprevalence of HBsAg and Anti-HCV. Hepatitis B vaccination is strongly recommended for our young populations.

Keywords

Hepatitis, prevalence, hepatocellular carcinoma, hepatitis B & C.

Introduction

Hepatitis C and B viruses (HCV and HBV) are among the principal causes of chronic liver diseases including cirrhosis related end stage liver disease and hepatocellular carcinoma. According to some reports there are about 170 million people with HCV infection and about 240 million people with HBV infection all over the world. Annually about 600,000 deaths are caused by HBV infection and about 3, 50,000 deaths by HCV infections worldwide. HCV and HBV infection is a global problem but it is rapidly spreading due to illiteracy, poverty and lack of community health education in developing countries. Most of these patients are asymptomatic and pose a great risk to population especially medical personnel. Both HCV and HBV infections are transmitted through blood and blood products but HBV infection is also spread by body fluids like vaginal secretions, saliva and semen.

Vaccine is available for HBV infection but not for HCV infection. Most of the HCV infected patients become chronic with considerable morbidity and mortality. Pakistan received a grant from the global alliance for vaccination and immunization (GAVI) in 2001-2002 that has enabled Pakistan to include HBV vaccination in routine expanded programme on immunization. Now in Pakistan HBV vaccination is part of EPI. Vaccination against HBV is very effective and confers protections against this chronic infections. HBV infection is 10 time more infectious than HCV infection and 100 times more infectious than HIV infection. The risk factors of these infections in our adults’ population are mostly unsafe injections and product products.

The rationale of our study is to know about the HBV and HCV status of young individuals applying for recruitment. If these infections do add to unemployment’s, preventive measures should be emphasized for their prevention.

Material and Methods

The study was carried out in Thall Scouts Hospital, Thall, which is located at the junction on North Waziristan Agency, Kurrum Agency and Orakzai Agency. Screening of recruits for hepatitis B and C in FC, KPK started in 2010. Induction of recruits occur about six monthly. So during this two and a half year study five batches were inducted and screened. We used (immunochromatography) ICT method (HCV kit name INTEC, China and HBV kit name ABON, China) for screening. The positive cases by ICT were sent to CMH Peshawar for confirmation by ELISA method. All the recruits were male with age group of 17 to 23 years. Recruits who were positive for HCV or HBV infections were counselled about the disease and were referred to medical specialist/ gastroenterologist.

Results

A total of 552 individuals were screened. All were male with
a mean age of 20.15 years (age range 17 to 23 years). Of 552 recruits on initial screening with ICT, HBsAg positivity was seen in 14 (2.53%) and Anti-HCV positivity was seen in 15 (2.71%). On retesting using ELISA, the HBsAg and Anti-HCV were detected in 19 individuals (3.44%). Of these 12 (2.17%) were positive for HBsAg and 7 (1.26%) were positive for Anti-HCV.

**Discussion**

In Pakistan most of the studies conducted till nineties were on healthy blood donors. Reports from studies done by Zuberi et al, Hashem et al yousuf et al and Rehman et al on volunteer blood donors showed the prevalence of HbsAg to be 3.1%, 0.99%, 1.11% and 5% respectively. Rahim et al and Zuberi et al also reported the prevalence of HbsAg in health care personnel to be 5% and 2.8%. However recent studies done on healthy blood donors in Pakistan showed prevalence of HbsAg to be around 3% to 3.5%.14

There is also great variation in the prevalence of Anti-HCV Antibodies in different part of the world. Some countries like Egypt have an extra ordinary high prevalence of HCV infection in some cities approaching 20% of population.15 The prevalence of HCV infection in European population is generally low. Study done on blood donors in Pakistan showed prevalence of around 5%.17

Risk factors for hepatitis B and C infection in Pakistan are multiple. Top of the list risk factors include use of injections for different diseases and blood product transfusions. Ignorance of barber regarding hepatitis transmission is also adding to this load. Sexual transmission may also play role but data regarding this mode of transmission is not available.9 There is no record available regarding hepatitis B vaccination of our population. There are myths about injections in our populations that’s it has cooling effect, recovery with injection is rapid and that fever relief is speedy. As the patients more willingly pay extra amount for injections, the health care providers also encourage such desire of patients. This is the reason that most of the people get unnecessary multiple injections in our set up; contributing to the load of hep Band C infections.18,19

**Conclusion**

HBV and HCV infections are an important cause of unemployment in this war affected areas as most of the recruits in FRONTIER CORPS come from FATA area, further adding distress to the area. To prevent hepatitis B infection in ours young population emphasis should be given on hepatitis B vaccination.

**Reference**

Evaluation of First Line Agents’ Resistance Amongst Campylobacter Isolates Using MIC Breakpoints at Aga Khan University Clinical Laboratory

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Abstract

Objective

Campylobacter is one of the most common causes of gastroenteritis especially in Pakistan, with an increasing drug resistance. Usually erythromycin and ciprofloxacin are considered the first line agents however, over a period of time, resistance against these antimicrobials has been observed in various regions of the world. Growing erythromycin resistance is of concern since these strains mostly turn out to be multi-drug resistant and there are very few options available to fight against them. The aim of the study is to evaluate frequency of erythromycin and ciprofloxacin resistance in Campylobacter species.

Material and methods

A total of 107 isolates were isolated from stool as well as blood samples from Jan 2014 to March 2016 and identified by conventional tests. Minimum inhibitory concentration (MIC) of erythromycin and ciprofloxacin was performed by using agar dilution method on 5% defibrinated sheep blood Mueller-Hinton agar plates as per CLSI recommendation. C. jejuni ATCC® 33560 is used as control for agar dilution testing.

Results

A total of 107 isolates were collected over the period of 2014 to 2016. Out of 107, 14.02% of the isolates were from blood samples while 88.5% were collected from stool. Seventy seven (77%) were C. jejuni while the rest were labeled as Campylobacter spp. Erythromycin resistance was 14%, ciprofloxacin resistance 93%. Of the 15 erythromycin strains, 11 were C. jejuni while 4 were Campylobacter spp. All 15 erythromycin resistant isolates were 100% resistance to ciprofloxacin.

Conclusion

There has been significant rise in resistance to first line agents in Campylobacter resulting in difficulty in identifying the better treatment option for Campylobacter and demanding the newer treatment options.

Key words

Campylobacter species, erythromycin, ciprofloxacin resistance

Introduction

Campylobacter is one of the most common cause of gastroenteritis in humans worldwide, especially in developing countries such as Pakistan where it is one of the leading cause of gastroenteritis.1 Though Campylobacter gastroenteritis is self-limiting, antimicrobial therapy may be required in severe cases of enterocolitis, immune-compromised population, pregnant females and extreme of ages.2 The mortality rate associated with invasive Campylobacter is estimated at 24 deaths per 10,000 culture confirmed cases or 200 deaths per year in the United States.3 Neurological and rheumatological sequelae are also serious post infection complications.2-4 Increasing drug resistance is presenting a challenge in the treatment of Campylobacteriosis. Erythromycin, a macrolide, and ciprofloxacin, a fluoroquinolone, are considered drugs of choice for its treatment. However, resistance against these antimicrobials has been observed worldwide.5,6 A study from Pakistan reported 47.5% quinolone resistance in their isolates.7 Similar quinolone-resistant pattern is also reported for Campylobacter isolates of North America (29%), Africa (41%), Europe (80%), Thailand (80%) and India (86.66%).5,6,8 Likewise, in a report from Pakistan, 2.9% of Campylobacter isolates were resistant to erythromycin.7 Growing erythromycin resistance is of concern since these strains mostly turn out to be multi-drug resistant.8

The aim of this study is to evaluate frequency of erythromycin and ciprofloxacin resistance in Campylobacter species.

Material and Methods

A total of 107 isolates were isolated from stool as well as blood samples from Jan 2014 to March 2016 at Pathology and clinical laboratory Laboratory Aga Khan University hospital (AKU). Samples at AKU laboratory are processed according to the American Society of Microbiology (ASM) guidelines. After initial isolation, identification is performed through conventional tests such as gram stain, catalase, oxidase and hippurate hydrolysis. Minimum inhibitory concentration (MIC) is performed by using agar dilution method on 5% defibrinated
sheep blood Mueller-Hinton agar plates as per CLSI recommendations. The MIC breakpoints used for resistance are those recommended by the Clinical and Laboratory Standards Institute (CLSI). Isolates were considered susceptible (S) intermediate (I) and resistance (R) based on these CLSI criteria (Table 1). The antimicrobials tested are erythromycin and ciprofloxacin (Sigma). *C. jejuni* ATCC® 33560 is used as control for agar dilution testing.

**Data Analysis**
The data was coded and analyzed by using Microsoft® Excel 2010 software. Frequency and percentage of the categorical variables i.e. gender, source of specimen (stool and blood), results of antimicrobial susceptibility (susceptible and resistant) for two agents (erythromycin and ciprofloxacin) were calculated.

**Results**
There were a total of 107 isolates of *Campylobacter* between Jan 2014 to March 2016 at AKU Laboratory. Out of 107, 14.02% (n=15) of the isolates were from blood, and 85.98% (n=92) were from stool samples. Seventy seven (77%) were *C. jejuni* while the rest were labeled as *Campylobacter spp*. Erythromycin resistance was 14% (15/107), ciprofloxacin resistance 93.4% (100/107). Of the 15 erythromycin strains, 11 were *C. jejuni* while 4 were *Campylobacter spp* as shown in Table 1. All 15 erythromycin resistant isolates were also resistant to ciprofloxacin.

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>Break points (µg/ml)</th>
<th>No. % of resistant strains n=107</th>
<th>Significance of difference in resistance rates (P value)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>S 4 I 8 R 16</td>
<td><em>C. jejuni</em> 11 4</td>
<td>0.735</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. spp</em> 73 20</td>
<td>0.082</td>
</tr>
</tbody>
</table>

*P value was calculated using Fisher's exact test.

**Discussion**
Campylobacteriosis is a food borne, self-limiting disease. Antimicrobials are given in cases of immune-compromised, pregnant females and extreme of ages. Quinolones and macrolides have been considered first line agents but rise in resistance in *Campylobacter* against these antibiotics has been attributed to use of antimicrobials in veterinary medicine. India have reported 86% to 97% of resistance to quinolones while another study from China reported up to 99% resistance in *Campylobacter coli* from animal origin. In 2010, less than half of the isolates in a study from Pakistan were resistant to quinolones, but in our study almost all were resistant, thus demonstrating a significant rise in resistance within 5 years. As a result of increasing quinolone resistance in *Campylobacter*, macrolides are now considered the treatment of choice. Our center reported 2.9% erythromycin resistance in 2007, with this study demonstrating a sharp increase. A study from Iran reported 77.7% of erythromycin resistance whereas a report from India showed 22.2% resistance to macrolides in 2013. Resistance has been seen to vary with regard to the species of *Campylobacter*. But in our study, as well as a 2013 study from India, there were similar rates of resistance in *C. Jejuni* and other species.

Previously, some studies have suggested that macrolide resistant *Campylobacter* strains are uniformly multidrug resistant (resistance to 3 or more drugs classes) and treatment is challenging. In our study only quinolone was tested and all our erythromycin resistant isolates were resistant to ciprofloxacin also. This raises concerns regarding treatment of these multidrug resistant *Campylobacter*. Effective results have been reported with carbapenems with excellent in vitro susceptibilities. However, further studies are needed regarding in vitro susceptibilities of erythromycin resistant *Campylobacter* to other antimicrobial agents.

In conclusion, there has been a rising trend in resistance of *Campylobacter* to erythromycin and ciprofloxacin. Further studies are required to evaluate new treatment options.

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Latent Tuberculosis Infection among Children under Five Years

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Abstract

Background
Latent tuberculosis infection (LTBI) is a significant public health problem. Despite the advanced diagnostic tools, the LTBI remains undiagnosed.

Objectives
To determine the frequency of LTBI and its predisposing factors in children under 5 years.

Methods
This cross sectional study was conducted in Out Patient Department (OPD) of National Institute of Child Health (NICH), Karachi from March 2014 to September 2014 after informed parental consent. All children under 5 year who attended OPD with symptoms like fever, cough of less than one week were screened. Children with strong suspicious of Tuberculosis (TB) were excluded. Medical factors contributing to LTBI such as family history of tuberculosis, BCG vaccination status and malnutrition on assessment were noted. Social factors including lack of parental education, passive smoking and overcrowding were also noted. All included children were given tuberculin skin test (TST) and an induration of ≥10 mm was considered positive TST.

Results
A total of 443 children were screened for LTBI during study period. Children’s mean age was 3.40 ±0.96 years. Illiteracy (88%), passive smoking (65%) and over crowding (24%) were social factors where as malnutrition (53%), positive family history (35%) and lack of BCG vaccination (71%) were medical factors found among screened children. LTBI was strongly correlated with age, weight, nutritional status and passive smoking (p-value <0.05).

Conclusion
LTBI was found in 3.83% of screened children with important contributing factors of illiteracy, passive smoking, malnutrition and TB in family.

Keywords
Latent Tuberculosis Infection, illiteracy, passive smoking, malnutrition

Introduction
Latent Tuberculosis Infection (LTBI) represents a substantial public health burden and is among the leading cause of infectious disease worldwide. More than one third population of the world is affected with latent infection. Tuberculosis is a leading cause of morbidity and mortality in all age groups in developing countries and Pakistan ranks 5th in the world among TB high-burden countries.

Childhood tuberculosis accounts for 10-20% of all cases of TB and it accounts for 8-20% of all deaths among children of high TB burden countries. Childhood TB is common but it is undetected and underreported, in many parts of the world particularly in South Asia. Data regarding childhood TB in Pakistan shows that only 4% are registered and 2.5% of children are at risk of acquiring infection. Among them 80-90 % of children develop LTBI and the risk of reactivation and development of primary progressive disease is 5-10%. This risk of progression is even higher in infants (30-40%) and young children (24%) younger than five years of age.

A close contact with active TB case, lack of BCG vaccination, undernutrition, small houses with large family size, under ventilated and poor sunlight exposure and smoking are possible predisposing factors among children with either LTBI or TB.

Children with LTBI represent the future reservoir for cases of TB and mostly under diagnosed or under reported. Thus, detecting and treating children with LTBI would be an important strategy for prevention of progression and elimination of TB. Establishing diagnosis of LTBI is problematic in children. Existence of active TB has

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been used as a surrogate for LTBI and various tools has been used for detection of LTBI. Though interferon gamma release assay (IGRAs) tests have been found highly sensitive (83-100%) for detection of active TB disease. But, TST is very inexpensive, easily available and commonly used screening test for detection of LTBI in developing countries in comparison to IGRAs tests which are very expensive, not standardized yet not easily available. Thus, the purpose of this study was to screen children for LTBI and common factors associated with LTBI so that recommendation may be made for prevention and control of childhood tuberculosis in the country.

**Patients and Methods**

This cross sectional study was conducted in Out Patient Department (OPD) of National Institute of Child Health (NICH), Karachi from March 2014 to September 2014 after informed consent from the parents/guardians. Institutional Ethical approval was taken. All children of age less than 5 years who attended OPD with symptoms like fever, cough of less than one week were randomly selected. Selected children were screened using tuberculin skin test (TST) and children with an induration of >10 mm were diagnosed as LTBI.

Physical Examination and Chest radiography was provided to all included patients. None of the children was reported for active pulmonary TB. Exclusion of active TB disease was done on basis of either symptoms or chest radiography or both. The presence of any symptom suggestive of TB (i.e. any one of cough >2 weeks, low grade fever of >2 week, night sweats, weight loss, chest pain, shortness of breath and fatigue) plus any abnormality on chest radiography highly suggestive of active TB. Confirmed latent tuberculosis infections were also enrolled in TB Clinic for treatment.

All children were evaluated for medical and social risk factors for LTBI. Medical factors such as family history of tuberculosis and close contact, BCG vaccination status and malnutrition (as assessed by using Modified Gomez classification) were noted. Social factors like lack of parental education, passive smoking and overcrowding were also noted.

A structured questionnaire was used to collect demographic data and possible factors contributing to LTBI. There are some potential confounders which may be responsible for either false positive or false negative TST results. These include prior BCG vaccination during last one year, recent or old TB infections, age less than 3 months, recent viral infections (chicken pox, measles, mumps, HIV), severe malnutrition, recent use of immunosuppressive drugs like steroids, faulty technique of TST administration, insufficient dose of purified protein derivative (PPD) and inactive tuberculin PPD. These confounders were controlled through sample selection. To avoid non response bias we used simple and of brief duration questionnaire.

**Statistical Analysis**

Data was analyzed using SPSS version 21. Descriptive analysis was done for socio-demographic variables. Bivariate analysis was run to see any effect of socio-demographics information on LTBI. Fischer exact test was applied after stratification of age, gender and weight with respect to LTBI and common factors. P-value = 0.05 was taken as significant.

**Results**

A total of n=443 children were screened during study period. Anthropometric measurements are shown of screened children are shown in Table 1. It shows that mean age of the patients was 3.40 ±0.96 years with majority of the children n= 298 (67%) were >3 years of age. Mean weight of the children was 10.69 ±1.71 Kg with majority n= 331 (75%) were >10Kg. Mean height of the children was 94.39 ±9.64 cm and majority of the patients n=305 (69%) were >95 cm. Females n=229 (52%) were slightly more than males n=214 (48%).

Out of 443 children screened, n=17(3.83%) children had LTBI. Table 2 shows socio-demographic and medical factors contributing to LTBI. Parental illiteracy n=15 (88%), history of passive smoking n=11(65%) and overcrowding n=4 (24%) were social factors whereas protein calorie malnutrition (PCM) grade II n=9 (53%), family history of TB n=6 (35%) and lack of BCG vaccination n=12 (71%) were the important medical contributing factors for LTBI. There was significant correlation of LTBI with age, weight, nutritional status and passive smoking (p-value <0.05).

**Discussion**

LTBI is a substantial public health problem. Approximately >1/3rd world’s population is infected with latent TB. Childhood LTBI is under diagnosed and under reported that may be due to lack of clinical symptoms and signs. In this study, we looked at the prevalence of latent tuberculosis infection in children younger than five years of age at our tertiary care hospital and possible risk factors attributable to LTBI.
LTBI is defined as a state of persistent bacterial infection controlled by body’s immune response in the absence of clinical symptoms of active disease.\(^1\) It is very important because this is a state of long-term bacillary containment in alveolar macrophages and extracellularly in granulomas that limits further spread and adjacent tissue destruction. There is a balance between pathogen and host but the correlates and mediators of this immune balance are not fully understood.\(^10,11\)

The LTBI has the highest prevalence in India, similar to that of active tuberculosis.\(^12\)

In our study, frequency of LTBI in children under five at tertiary care center was found to be 3.83%. This is similar to reported prevalence of LTBI of 3.5% and 4.7% in 1-5 year and school age children from Iran and China respectively.\(^13,14\)

The overall life time risk of LTBI reactivation is approximately 5-10% among older children but risk of progression to active disease is higher in younger children.\(^15,16\) Childhood infection establishes the reservoir for outbreaks in the future so it is important to make proper diagnosis and treatment of LTBI in the endemic region for Tuberculosis control.\(^17\)

There are many socioeconomic and medical factors which predispose to latent TB such as low family income, illiteracy, poor housing and overcrowding, passive smoking, living in close contact with active TB patient, lack of BCG vaccination and access to medical access care. In addition, undernutrition, measles and HIV are also important medical conditions which predisposes a child to LTBI.\(^7,9,17,19\)

In this study, we found high frequency of social factors like illiteracy (88%), passive smoking (65%) and overcrowding (24%). Nguyen TH et al highlighted the importance of contact tracing in remote settings with high TB prevalence.\(^3\) Similarly den Boon et al from South Africa suggested that passive smoking may also be responsible for the increased risk of acquiring TB infection.\(^19\)

In this study, we used TST for the diagnosis of LTBI similar to Nguyen et al, Iskander et al and Okeda et al.\(^2,21,22\)
Overall control of TB infection depends on the detection and preventive treatment of LTBI, thus halting the progression of LTBI to disease. Rutherford ME et al has suggested that there is underutilization of WHO guidelines in TB endemic areas, which promotes active screening and preventive therapy for children under 5 years of age. In our study, the screening in children less than 5 years and their management is small step towards WHO guidelines.

In this study, the identified factors including parental illiteracy, history of passive smoking, overcrowding, grade II PCM, family history of TB, lack of BCG vaccination were the social and medical contributing factors for LTBI. This information may facilitate policy makers for public health planning and policies in the community for control of TB in our country.

This study supports the importance of contact tracing activities in the control of TB in developing countries, associated with early case detection and treatment.

Limitation of Study
This is a small study from single tertiary care center over a short period in population below 5 years. It cannot be generalized since it has not been carried out in a community with large number of children and adolescent. However, we think that it is a good start to develop trends in screening and management of LTBI before development of active disease.

Conclusion
The prevalence of latent tuberculosis infection was 3.83%. We found a high prevalence of parental illiteracy (88%), malnutrition (53%), family history of TB or close contact (35%) and overcrowding (24%). These may be attributed to LTBI. However, further studies on prevalence of LTBI and implementation of WHO guidelines are required in our country for better control of LTBI and thus ultimately decreasing burden of active TB.

References
Methicillin Resistant Staphylococcus Aureus Causing Pyopneumothorax in a Child

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Abstract

Methicillin Resistant Staphylococcus Aureus Causing Pyopneumothorax in a Child

Initially described as hospital-acquired, methicillin-resistant Staphylococcus aureus (MRSA) has emerged as a significant community-acquired pathogen as well, causing serious infections, even in children. In the past decade, there has been a substantial increase in its prevalence, attributable to distinctive genotypes that appear to have evolved in the community. We describe a previously healthy boy presenting with pyopneumothorax caused by community-acquired MRSA.

Keywords

pyopneumothorax; community-acquired MRSA; MRSA in children

Introduction and Rationale

Case History

A 20 month old boy, previously healthy, was brought to the emergency department by his mother with the complaints of fever and cough for 1 week, progressing to shortness of breath for 2 days. Fever was initially low grade. Cough was sporadic and non-productive. The patient took oral antibiotic prescribed by his pediatrician with no improvement. There was no history of choking. No history of allergies. His immunizations were up to date. The child lives in an extended family environment. His grandmother was recently treated for a lung infection for which she was hospitalized but no further detail was available.

On presentation, the patient was in severe distress, febrile at 104°F and fussy. He was also tachycardic and tachypneic, oxygen saturation 73% on room air. Chest examination revealed subcostal retractions, decreased air entry on the left side, and crackles in the left lower lung. The patient was started on oxygen by nasal cannula without much improvement. Empirical intravenous ceftriaxone and vancomycin was started, and chest X-ray requested. Chest x-ray (Figure 1) confirmed a pneumothorax with collapsed left lung. Emergency intervention to expand the lung by inserting chest tube resulted in improved oxygenation. The straw colored pleural fluid was sent for analysis and culture.

The child was admitted on the pediatric floor. Fluid analysis revealed a PH of 8.0, RBC’s 2+, cell count of 1977/mm³ with 80% neutrophils, 2.9 g/dl proteins, <5 mg/dl of glucose and an LDH of 1616 u/L. Intravenous antibiotics were continued in hospital and serial chest x-rays done. The fever settled by the 5th day but tachypnea continued, therefore, computerized tomography of chest (Figure 2) was done which revealed mild left pyopneumothorax with collapse/consolidation of underlying left lung, and also right lung base collapse. Chest physiotherapy was started. Pleural fluid culture grew methicillin resistant Staphylococcus aureus (MRSA), resistant to amoxicillin/clavulanic acid, cloxacillin and cephalozin; but sensitive to vancomycin, sulfamethoxazole (co-trimoxazole), fusidic acid, clindamycin, minocycline and linezolid. Unfortunately, genotyping of the bacteria is not available in our laboratory, therefore was not done. Acid fast smear was negative. Blood
culture did not show any growth. By the 11th day of admission the chest tube was removed with interval improvement on chest x-ray. The boy was discharged home on oral co-trimoxazole, chosen due to its cost benefit compared to linezolid. He was seen in the thoracic surgery clinic one week later for follow up of the chest drain site, and was doing well. Two weeks after discharge, he was seen in the pediatric clinic and continued to remain well. He completed four weeks of total treatment (intravenous plus oral) as advised by the infectious disease team.

Discussion
Methicillin-resistant Staphylococcus aureus (MRSA) has become a prominent pathogen in the pediatric population. The epidemiology of MRSA infections is complex. Infections are often categorized on the basis of where they were acquired: hospital or community acquired. There are several other features that distinguish these two types of infections. These two strains of MRSA cause different types of infections, have dissimilar genetic profiles, produce different virulence factors, and often have unique antibiotic susceptibility patterns. Approximately, 20–40% of normal individuals carry at least 1 strain of Staphylococcus aureus in the anterior nares at any given time, and serve as a reservoir for transmission.

Acquisition of the organism in a hospital or a long-term care facility is well documented, termed as hospital-acquired (HA MRSA) or nosocomially acquired (NA MRSA). Predisposing risk factors for HA MRSA infections in pediatric populations include prolonged hospitalization, invasive or surgical procedures, indwelling catheters, endotracheal tubes, and prolonged or recurrent exposure to antibiotics, factors similar to those documented in adults. HA-MRSA is more likely to cause infections of the bloodstream, urinary tract, surgical site and ventilator-associated pneumonia.

Community acquired MRSA (CA MRSA) infections have gained prevalence in the pediatric population in the last decade. CA MRSA infections were initially described in children with bloodstream infections and no prior health care exposure. The term “community-acquired MRSA” has been used to describe MRSA infection diagnosed outside of the hospital or within 48 to 72 hours of admission, although the definition is not fixed. Community strains of MRSA may arise in either of two ways: (1) derived from hospital strains which were carried into the community, and spread person to person in settings with overcrowding; frequent skin-to-skin contact; sharing of personal items, or (2) community MRSA may arise de novo when the methicillin-resistance gene complex is acquired by a methicillin-susceptible strain. CA MRSA infection commonly presents as pyogenic skin and soft-tissue infections in previously healthy individuals, which may be recurrent, and often affect the lower extremities and buttocks, leading to cellulitis. Severe invasive disease has also been reported.

The diagnosis depends on isolation of the organism from abscess cavities, blood, and tissue aspirates. Surface swab cultures are not useful as they may reflect surface contamination. After isolation, identification is made on the basis of Gram stain and coagulase activity. Methicillin resistance is determined by the presence of a penicillin-binding protein with decreased affinity to penicillin. The mecA gene encodes this protein and is located on the staphylococcal cassette chromosome mec (SCCmec), which is a mobile and transferable piece of genetic material. Five distinct SCCmec types have been identified, and they are labeled SCCmec I through V. CA MRSA infections have mostly been associated with type IV SCCmec, as demonstrated in Pakistan as well, while hospital-associated strains are more likely to contain SCCmec type II or III. In addition, virulence factors such as the Panton–Valentine leukocidin, have been implicated in tissue destruction. The Panton–Valentine leukocidin genes ( lukSF-PV) code for cytotoxin production that causes tissue necrosis by forming pores in cell membranes, especially in neutrophils.

Community-associated strains are often resistant to β-lactam antibiotics, but retain their susceptibility to many other classes of antimicrobials such as sulfamethoxazole/trimethoprim (SMZ/TMP), clindamycin, tetracyclines, and gentamicin. Hospital-associated strains, however, are often multi-drug resistant and require the use of vancomycin or newer agents such as daptomycin, linezolid, or quinupristin/dalfopristin. Clinicians should be knowledgeable about antimicrobial agents for empirical use such as those mentioned above, with intravenous vancomycin employed in severe cases. Tetracyclins should be avoided in children due to adverse affects on skeletal development.
For outpatients with purulent cellulitis or skin and soft tissue infections, empirical therapy for CA-MRSA is recommended pending culture results.\textsuperscript{10} Empirical therapy for infection due to \(\beta\)-hemolytic streptococci is likely to be unnecessary. Duration of therapy depends on the site and severity of infection, whereby 5-10 days is recommended for outpatient therapy and 2-6 weeks are recommended for endocarditis, osteomyelitis, necrotizing pneumonia, or complicated bacteremia.\textsuperscript{3,10} After initial parenteral therapy and documented clinical improvement, completion of the course with oral drug can be considered. For endocarditis and CNS infection, parenteral therapy is recommended for the entire treatment. All abscess cavities should be drained and all foreign bodies should be removed, if possible.\textsuperscript{10} All patients with culture positive MRSA bacteremia, with or without sepsis, should be evaluated for endocarditis with echocardiography.\textsuperscript{3}

Our case is presumed to be community-acquired as the patient had no previous hospital associated risk factors and the culture susceptibility pattern was closer to most community-acquired strains. Genotyping of the organism is required for further supporting the diagnosis.

MRSA infections are on the rise. It has been hypothesized that these infections could be prevented if nasal colonization with Staphylococcus aureus was eradicated. However, eradication of nasal carriage is difficult, and resistant strains can emerge, therefore, this treatment is not recommended for routine use.\textsuperscript{5} The strongest recommendations for prevention of infection are merely standard infection control procedures and good hand hygiene practices.\textsuperscript{3,5}

References
INSTRUCTIONS FOR AUTHORS

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.

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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.

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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.

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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.

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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.

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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.
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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.

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