Original Article

The pattern of antibiotic resistance of Streptococcus pneumoniae isolated from sputum of patients with respiratory infection

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ABSTRACT

Introduction: Nowadays antibiotic resistance is one of the problems faced by all countries. Last year, the World Health Organization mentioned that pneumococcus and meningitis are the most common causes of respiratory tract infections, thus, this study aimed to evaluate the antibiotic resistant pneumococcal disease. Methods: In this study, the prevalence of antibiotic-resistant Streptococcus pneumoniae was studied by culturing infections in patients admitted to Shohada Ashayer hospital clinic from winter, 2002 to spring, 2003. Patients with upper and lower respiratory tract infections were studied through the examination of their sputum specimens obtained from throat swabs, and in the biphasic phase, the samples were placed and transported to the laboratory after the initial culture in specific chocolate agar medium. Pneumococcal susceptibility reaction chemistry was used by in vitro disk diffusion method in antibiotics medium. Results: From 125 patients' cultures with respiratory infections, 34 patients (27.2%) were positive for pneumococci, of whom 60% were men with an average of 21.13, and 40% were women with an average of 35.22. The results of antibiogram by disk diffusion method was performed on antibiotics resistance rates of pneumococcal sensitivity as follows: the highest resistance to antibiotics was found for ceftizoxime with 100%, the lowest resistance for nitrofurantoin with 6.45 %, the highest sensitivity to antibiotics for nitrofurantoin with 93.54%, and the lowest sensitivity for ampicillin with 3.3%. Conclusion: An increase in pneumococcal resistance to most antibiotics may be necessary, so the primary and secondary prevention measures are to set a guideline to be approved in a country for the rational use of antibiotics.

Keywords: Pneumococcal, pneumonia, antibiotics resistance

Introduction

Streptococcus is a variety of gram-positive bacteria that is observed in pairs or chain, and can be of the most common types of Streptococcus pyogenes, pneumococcus, Streptococcus intermedius and Streptococcus mutans [1]. The bacterium pneumonia was first discovered in the year 1881 by Steve George in America, and Louis Pasteur in France. The bacterium was named Diplococcus pneumonia in 1920, due to its chain-like growth in liquid media, and in 1974 it was renamed as Streptococcus pneumoniae. In 1928, Frederick Griffith inoculated live pneumococcus without capsules (Non-pathogenic) at the same time together with killed pneumococcus with capsules (pathogenic) in mice, and pneumococcus without capsule became encapsulated and pathogenic (transformation). In 1944, three scientists, namely Avery, MacLeod and McCarthy showed that a factor, which is present in encapsulated pneumococcus without capsules, was DNA, and this has transformed the pneumococcus without capsules into those with capsule. With this research, molecular genetics era began [2].

Streptococcus pneumoniae, or pneumococcus is one of the most common gram-positive streptococci, it has a coco narrow lancet-shape which is in pairs or in short chains, and most encapsulated bacteria are generally facultative anaerobic, and nutritional needs are very great [3]. Pneumococcus is usually in the throat and pharynx of healthy people, about 5-75% of people are in the carrier state [4, 5], and it is one of the most important pathogenic bacteria in humans. The bacterium is the

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main cause of pneumonia disease [6]. This bacterium can cause other infections such as sinusitis, acute otitis (middle ear infection), bacteremia, sepsis, meningitis, osteomyelitis, septic arthritis, endocarditis, peritonitis, pericarditis, cellulitis, and also causes brain abscesses [7]. Pneumonia caused by pneumococcal lobar is also called pneumonia. Middle ear infections caused by pneumococcus dramatically increase the levels of interleukin-10, and they can be used as diagnostic biomarkers [8].

Pneumococcus is the main cause of bacterial pneumonia (about 500,000 in America per year), meningitis (about 6,000 per year), acute otitis and sinusitis (< 7 million cases per year), and bacteremia (about 55,000 per year) [9]. These diseases are common in children and elders because the two groups, at a specific time, have a low pneumococcal capsule polysaccharides calcium [10–12]. On the other hand, this bacterium can be seen in 25-30% of patients with pneumococcal pneumonia, and more than 80% of patients with meningitis, and bacteremia occurs commonly in patients with sinusitis and acute otitis [13, 14].

Pneumococci are one of the main causes of invasive infections (12-17 cases per 100,000 people) [15], and the most vulnerable are children younger than 5 years, elders over 60, and people with chronic underlying medical conditions such as diabetes, chronic obstructive pulmonary disease (COPD), and immune deficient patients [16, 17]. Pneumococci living in the upper airways of most normal people can become aggressive. More than 90% of 6-month to 5-year old people have their nasopharynx infected with pneumococci. It is the most common cause of acute otitis and middle-acquired pneumonia, and one of the most common causes of meningitis in the community [18]. The highest incidence of meningitis in infants was 3-5 months, and in the case of otitis media 6-12 months, and in the case of hospitalization due to pneumonia it was 13-18 months. Widespread vaccination by 7 valent pneumococcal reduces the number of people that are carriers of this organism in the nasopharynx, and therefore pneumococcal infections have been reduced. It is pneumococcal serotype 90. When a type with capsule is present, there is a possibility of causing serious illness in humans. Serotype 19F, 23F, 4, 6B, 9V, 14 are invasive species in children, and of these, 6B, 9V, 19F and 14 often are not sensitive to penicillin. Infection is more common in males than female [19]. Pneumococcal disease is often caused by respiratory viral infection. Pneumococcal disease is caused by sporadic and respiratory droplets transferred from one person to the other [20].

Following the discovery of antibiotics such as penicillin and cephalosporin, and promotion of their clinical use during illness, complications of the disease clearly fell parallel to the aftermath of the overuse of antibiotics [21]. The exponential growth trend of antibiotic resistance was found, including the associated risk factors in this area, which can be age, immune deficiency, prolonged antibiotic use, living in crowded places and prolonged contact with the corresponding treatment-resistant patients with chronic infections [22–25].

In the years 1950-1970, only a few cases of resistance to antibiotics in penicillin family was reported in Africa and Spain (less than 5%) [26–28]. The reasons werse due to inappropriate prescription of antibiotics, and immigration of Africans to the United States of America with resistance to penicillin; day to day activities further added to penicillin resistance [29]. Numerous reports of resistance to the cephalosporin and vancomycin are less commonly reported [30–33].

In this study, the prevalence of antibiotic-resistant Streptococcus pneumoniae was studied by culturing the infections of patients admitted to Shohada Ashayer hospital clinic from winter, 2002 to spring, 2003.

Methods

All the patients with upper and lower respiratory tract infections were referred to Shohada Ashayer hospital clinic from winter, 2002 to spring, 2003.

Sample size

The minimum sample size was 323, but according to the census procedures we sampled more than the mentioned figure.

Sampling

The census sampling method was applied. The execution method (if not using the attached questionnaire) was as follows: Patients with upper and lower respiratory tract infections were referred to Shahid Ashayer hospital clinic to be examined by a doctor for current and past medical history of signs of infections, throat swabs from the patients' sputum samples were prepared, the samples were placed in biphasic and transferred to the laboratory. After the initial culture in specific medium, and then antibiotic chocolate agar, the method of pneumococcal resistance to antibiotics was studied. Symptoms of pneumonia include any patient with purulent sputum after cough with pleuritic chest pain with or without fever during the past two weeks. Symptoms of sinusitis patients include patients with either acute and chronic headaches, or pain in the forehead during prostration, and postnasal mucus, or previous history of headache with sinusitis or sinusitis view under CT scan, a history of heart disease and diseases including COPD, diabetes, recurrent pneumonia, and chronic sinusitis. There are various methods for determining the susceptibility of bacteria to antibiotics, but, we will introduce a simple routine test and disk diffusion method in this study.

After isolating the bacteria, some bacteria colonies by Anas (no loops) are removed, and we dissolve the sterile saline solution. It should be noted that since the antibiogram turbidity test is very important to us, we must be careful in the selection of the sample so that it does not take more or less than half McFarland. If the McFarland turbidity is less than half the amount of sample dissolved in saline, or if turbidity is more than half McFarland, we need some added saline to reach the appropriate opacity equal to half McFarland. After the preparation of homogeneous solution, with a sterile swab to the stirred solution, we rinse the swab (for rinsing, swab with force using water and lean against the pipe wall). It was transferred to

Mueller Hinton medium, and swabbed completely with cotton. The culture was grown so that no local environment effect on it was found. After the cultivation, disc susceptibility testing was done half an hour before removing it out of the fridge and transferred on the culture. The disk is placed on Mueller Hinton medium with a circular distance of about 12mm from one another, and must be separated from the wall. According to our experience, the disc distance can be low or high.

The discs used must be appropriate for the type of bacteria isolated, for example, never gram-negative bacteria. We are not resistant to use penicillin or chloramphenicol antibiotics for urinary tract infection, not because these antibiotics cannot enter the urinary tract. After loading the disc, the plates were closed for 24 hours at a temperature of 37 ° C incubation (It should be noted that, due to the authors' new research, the temperature dropped to 35 ° C and duration of incubation dropped to 16 to 18 hours).

After 24 hours, the plates are checked under lights. The inhibition zone diameter was measured with a ruler and the table with discs, and drug susceptibility testing report was provided for each of the antibiotics, for susceptibility, resistance, and/or being intermediate.

Reading and Reporting

After incubation, our culture environment should be as follows (Figure 1):

As shown, there are some hollow spaces around the discs reflecting the sensitivity of those bacteria; susceptibility to disk was reported. Also there are no hollow spaces around some other discs. In this case, the bacteria had resistant towards it. When none of the above observations is found, then, semi-sensitivity was reported.

Antibiotic medium

Environment disc used in Muller Hinton

A pH between 7.2-7.4 was set. At the plate with a diameter of 100 mm, we poured 25-30 ml Mueller Hinton around the environment. To avoid drying, surface plate should be stored in plastic bags. After the inoculation of antibiotic medium at 15 minutes interval, antibiotic discs were checked for the agar surface distance. It was incubated 35 ° C for 16-18 hours before storage. Fastidious bacteria modified methods in another way is also difficult to grow bacteria in some of the specific culture medium used, such as HTM in Haemophilus.

Results

125 cultures from people with upper and lower respiratory infections (sinusitis and pneumonia) referred to Shahid Ashayer hospital clinic by sampling swab of throat secretions culture were examined. The test of 34 patients (27.2%) was positive to pneumococcus by antibiogramed disk diffusion method following antibiotics. Of the total positive pneumococcus, 18 patients (52.9%) were male subjects and 12 patients (35.3%) were female, and 4 patients (11.8%) were in unknown form.

The mean age of the positive pneumococcus samples in the men was 21.13, and the standard deviation was 15.84. The mean age of the positive pneumococcus samples in the women was 35.22, and the standard deviation was 17.06. Of the total positive pneumococcus cases, 93.54% subjects were sensitive to the antibiotic nitrofurantoin, 6.45% were resistant. 81.3% of the individuals were sensitive to antibiotic cefaclor, and 12.5% were resistant, while 6.3% were intermediate. 46.7% of the individuals were sensitive to antibiotic clindamycin, 46.7% were resistance, while 6.7% were intermediate. 83.3% of the individuals were sensitive to antibiotic vancomycin, and 16.7% were resistant. 40% of the individuals were sensitive to antibiotic penicillin, and 60% were resistant. 44.4% of the individuals were sensitive to antibiotic erythromycin, 40.7% were resistant, while 14.8% were intermediate. 30% of the individuals were sensitive to antibiotic tetracycline, 56.7% were resistant, while 13.3% were intermediate. 3.3% of the individuals were sensitive to antibiotic ampicillin, and 96.7% were resistant. 50% of the individuals were sensitive to antibiotic norfloxacin, 39.3% were resistant, while 10.7% were intermediate. 100% of the individuals were resistant to antibiotic ceftizoxime. 46.7% of the individuals were sensitive to antibiotic sulfamethoxazole, and 53.3% were resistant. Of the total of the 27 positive pneumococcus cases, 87.1% were resistant to antibiotic ciprofloxacin and 12.9% were intermediate. 90% of the individuals were sensitive to antibiotic oxacillin, and 10% were resistant. The highest resistance was found to antibiotic ceftizoxime with 100%, and the lowest resistance to nitrofurantoin with 6.45%. Also, the highest sensitivity was found to nitrofurantoin with 93.54%, and the lowest sensitivity to ampicillin with 3.3% (Table 1 and Figure 2).

Discussion

The positive pneumococcus carriers in this study among the men with a mean age of 21.13 and the women with a mean age of 35.22 in the city of Khorramabad were 27.2%. of these, 60% were male and 40% were female. In a study by Fatimeh et al. carried out in the University of Shahid Sadovaghi, 51% were male and 49% were female, their ages ranged from 7 to 65 months, and 37.5% were carriers of pneumococcus. In the present study, we studied the reason why carriers of pneumococcus are more children than adults.

In a study carried out on 4936 patients, from January 1998 to March 1999 in 11 countries including Asia and Middle East, as the biggest study on the prevalence of pneumococcus carriers, the average was 22.3% and the highest rate in Indonesia was 43.2% [34]. In the present study, the prevalence of the carriers is slightly higher than this amount, and this is probably due to the fact that our sampled patients were admitted to the hospital.

In a study conducted in Shiraz, pneumococcus strains susceptibility to penicillin was 66.1%, semi-sensitive was 18.3%, and resistance was 15.6%. The study in comparison with the sensitivity study gave a higher resistance to penicillin, and half were less sensitive [35]. In Carolina, 44.9% of pneumococci were sensitive to penicillin, 33.2% were semi-sensitive, and 11.7% were resistant [36]. In Australia, 48% of

pneumococcus strains were sensitive, 14% were semi-sensitive, and 38% were resistant to penicillin [37]. In France 20% of pneumococci were resistant to penicillin [38]. In an article from America, about 24% were resistant to penicillin [39]. A study in Imam Khomeini Hospital, Tehran University of Medical Sciences, Mehr et al. studied pneumococci resistance to penicillin and other antibiotics and found that 47 were sensitive and 19 were resistant [40]. In a study by Fatimeh et al., it was reported that 50% resistance was observed for penicillin. In this study, 60% penicillin resistance as compared to other studies is due to differences in regional population, as well as differences in the prevalence of antibiotic penicillin [41].

In a study in Tehran for 57 positive cultures, 70% were resistant to pneumococcus. MIC survey reported all pneumococci were resistant and sensitive to vancomycin and ceftriaxone, and only a limited number of intermediate resistance to penicillin and erythromycin, and chloramphenicol resistance to co-trimoxazole was reported [42]. In Fatimeh et al.'s study, it was reported that resistance to erythromycin was 62.5%, ciprofloxacin was 4.2%, tetracycline was 30.6%, ceftizoxime was 5.6%, cephalexin 15.3%, and co-trimoxazole was 62.5%.

Iftaqar et al, in their study conducted in 1997-1998, from 60 pneumococci samples isolated from patients, resistance to ampicillin, amoxicillin and cefazolin by disk diffusion method was 7.5, 6.1 and 10.81 respectively. In our study, penicillin resistance was 60%, erythromycin was 40.7%, tetracycline was 56. 7%, ceftizoxime was 100%, and ampicillin was 96. 7%. The difference in resistance can differ with time and region. In the present study we concluded that antibiotic resistance rates are increasing, and the region-to-region resistance in the country, even a city can vary in different hospitals [43].

In the study by Mahdi et al. in Mashhad on 102 patients, 8.78% were cultured, the resistance to antibiotics was 100%, 80.4%, 43.13%, 40.19%, 22.55% 48.03%, 18.62% for cotrimoxazole, erythromycin, cefixime, amoxicillin, penicillin, amoxicillin, and chloramphenicol respectively. All the 54 samples had positive cultures from pneumococcus isolates, which indicates the presence of lytA gene for pneumococci. In the E-test, all beta-lactam resistance was high [44]. The resistance was remarkable even to the new generation and all the strains were susceptible to vancomycin and ciprofloxacin. Mutation in the beta-lactam resistance genes and macrolides E-test results was confirmed [45]. While in our study microbes in antibiotic nitrofurantoin show a positive pneumococcus in 45.6% of the total population, 12.5% for cefaclor, 26.7% for methicillin, 46.7% for clindamycin, 16.7% for vancomycin, 39.3% for norfloxacin, 53.3% for sulfamethoxazole, ciprofloxacin for 87.1%, and 90% for oxacillin [46].

In further studies on how to follow pneumococcal infections and antibiotic resistance, for the most common pathogens responsible for pneumonia (20-60% items), community-acquired pneumococci were introduced, so that 11-20% of community acquired pneumonia-related deaths was accounted [47]. Specific antibiotics have been used for the treatment of streptococci and pneumococci, such as penicillin, and unfortunately, in recent decades in the chaotic and ever-increasing use of the drug, resistance to penicillin and cephalosporin has been observed. In 1960, the reported cases of resistance to penicillin were limited to Africa and Spain, with less than 5% of the cases, respectively (42-41), but in the years 1990 to 2000, the reports for antibiotic resistance in Europe, Latin America and North America were 14.7%, 12. 7% and 15.9%, respectively. Increasing trend in recent years has unfortunately continued in 2005, more than 30% of pneumococci are resistant to various antibiotics, most associated complications among children less than 5 years have shown that the following studies were designed to evaluate how to reduce antibiotic resistance among pneumococci. Conjugate vaccine approaches can reduce the rate of resistance to penicillin by about 35% and the risk of invasive pneumococcus infections in children less than 2 years decreased by about 69% [48].

A more comprehensive study on the situation of antibiotic resistance to other antibiotics shows the growing trend of antibiotic resistance in pneumococci to antibiotics such as penicillin, ceftriaxone, azithromycin, trimethoprim-sulfamethoxazole, vancomycin in the United States of America. According to the study, about 65% of pneumococcus infections (except the infections of the central nervous system) were treated with penicillin, relative resistance of which was 17%, and 17% were also more resistant to amoxicillin among the patients treated, and an appropriate response to treatment was 93%, while 5% and 2% of relative and full strength was reported respectively [49].

Following the call to treat infections of the central nervous system, penicillin and ceftriaxone gave 65% and 90% resistance respectively and 35% and 10% (7% and 3% relative resistance and full resistance) were reported [50, 51].

Further studies have been done on the antibiotic resistance in pneumococci to other antibiotics and the following results were reported; 25% pneumococci to macrolides in general, 15% to clindamycin, 30% to trimethoprim-sulfamethoxazole, 18% to doxycycline and 2% to new generation of quinolones drug resistance antibiotic. In a more comprehensive evaluation of genetic variations resistant to macrolides and clindamycin, about 1/3 of macrolides and clindamycin resistant pneumococcus (ERMCB) are microorganisms that are more common in Europe. On the other hand, isolating the patients can somewhat reduce resistance to macrolides [52].

Studies in other countries assessed the comparison of antibiotic-resistant pneumococci in Canada which was less than that of the United States, but more than Eastern Europe, and most of antibiotic-resistant pneumococci in the United States are due to the increasing use of fluoroquinolones, and quinolones. Therefore, in these studies, doing epidemiological studies is a further recommendation to implement the spread of antibiotic-resistant pneumococci and effective strategies for reducing antibiotic resistance throughout the country [53–55].

Conclusion

To begin the treatment of pneumococcus infections, penicillin and other antibiotics such as ceftizoxime, ciprofloxacin, tetracycline, ampicillin, and oxacillin are not desirable due to their high resistance against pneumonia drugs, and it is better to present the culture and susceptibility in respiratory tract infections. The third generation cephalosporin for brain infections such as meningitis, and the third generation vancomycin can be used.

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Table 1: The antibiotics studied with percentages of resistance, sensitivity and intermediate

antibiotics			
Nitrofurantoin	6. 45	93. 54	0
Cefaclor	12.5	81.3	6.3
Methicillin	26.70	66. 7	6.7
Clindamycin	46. 70	46. 7	6. 7
Vancomycin	16.70	86. 3	0
Penicillin	60	40	0
Erythromycin	40. 70	44.4	14. 8
Tetracycline	56. 70	30	13. 3
Ampicillin	96. 70	3.3	0
Norfloxacin	39. 30	50	10. 7
Ceftizoxime	100	0	0
Sulfamethoxazole	56. 30	46. 7	0
Ciprofloxacin	87. 10	12. 9	0
Oxacillin	90	10	0

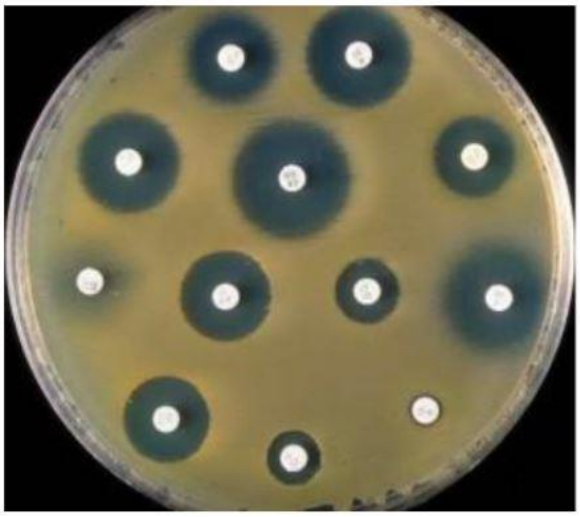

Figure 1: Culture incubation on plate

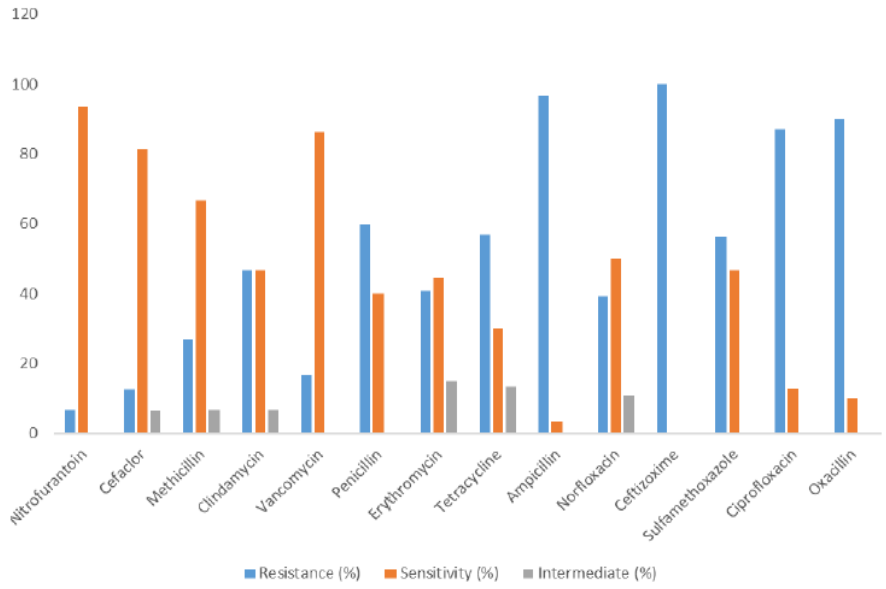

Figure 2: