Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2015; 3(2B):654-657 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2015.v03i02.025

Case Report

The Increasing Trend of Multi Drug Resistant *Streptococcus pneumoniae* in India: Case Report with Supporting Review of Literature

Rajendran T.[1*], Jeremiah S. S.[2], Vijaykumar G. S.[3], Muthaiah M.[4]
[1]Assistant Professor, [2]Assistant Professor, [3]Professor and Head, [4]Professor , Department of Microbiology, Velammal Medical College Hospital and Research Institute, Madurai – 625009, Tamilnadu, India

***Corresponding author**
Dr. Rajendran T
Email: rajt1960@gmail.com

Abstract: *Streptococcus pneumoniae* is an organism known to cause respiratory tract infections which can lead to serious life threatening complications. Although these infections can be readily treated with antibiotics, drug resistance in *S. pneumoniae* poses a significant threat. Multi drug resistant strains of *S. pneumoniae* which emerged over a couple of decades ago were almost absent in India till the recent years. However, the prevalence of these strains is on the rise in our country. We report a case of community acquired pneumonia caused by a multi drug resistant strain of *S. pneumoniae* serotype 19F and summarize the rising trend of multi drug resistance in pneumococci with a concise review.
Keywords: Multidrug resistant *Streptococcus pneumoniae*, Serotype, Community acquired pneumonia.

INTRODUCTION

Streptococcus pneumoniae is one among the bacterial causes for a high global mortality rate. With the ability to cause serious life threatening infections such as pneumonia, meningitis and septicaemia, *S. pneumoniae* is responsible for over one million deaths every year across the world. Next to acute diarrheal disease, pneumonia is one of the leading causes of child deaths in India of which *S. pneumoniae* accounts to nearly one fourth of the etiology [1].

This setting would be further complicated if pneumococcal strains acquire resistance to the commonly used antibiotics. Although widespread resistance to penicillin and macrolides occurs commonly in Asian countries, their frequency is still comparatively low in India [2]. The situation is now changing, as isolated penicillin, macrolide and cotrimoxazole resistant pneumococcal strains are increasingly being reported from India. Also, multi drug resistant *S. pneumoniae* (MDR-SP) which has been a very rare entity so far, is now on the rise in our country [3].

In this context, we report a case of community acquired pneumonia caused by MDR-SP which was treated with fluoroquinolones. However, subsequent review of literature reveals a gloomy state of the scenario of MDR-SP in India.

CASE REPORT

A 17 year old male patient, who was a known case of situs inversus with no significant co-morbidities, came to the general medicine out-patient department with complaints of fever and cough with expectoration of purulent sputum for five days. He had no history of treatment elsewhere and had not visited any health care facility for the past two months. There was no history of travel to other countries. Chest auscultation revealed bilateral crepitations leading to the clinical diagnosis of community acquired pneumonia. Sputum was collected for microbiological analysis and the patient was empirically started on treatment with oral levofloxacin.

Microbiological testing of sputum sample revealed lanceolate shaped Gram positive cocci in pairs in the direct smear. Culture on 5% sheep blood agar produced alpha hemolytic colonies with a typical draughtsman appearance. Susceptibility to optochin and solubility in bile confirmed the identification of *S. pneumoniae*. Antibiotic susceptibility testing (AST) was performed using the disc diffusion method and confirmed with automated minimum inhibitory concentration (MIC) testing. The procedures and interpretation were done as per the guidelines of clinical and laboratory standards institute (CLSI) 2013. In the disc diffusion testing, the isolate did not show any zone of inhibition to three antibiotics of different classes namely oxacillin, erythromycin and cotrimoxazole.(Figure 1) As the CLSI advocates MIC testing for interpreting the susceptibility of *S. pneumoniae* to beta-lactam antibiotics, the MICs of the

isolate for the 'Gram positive *S. pneumoniae* panel' of antibiotics were obtained using the Vitek-2C automated instrument (Table 1) .The isolate was found to be a MDR-SP strain as it was resistant to more than three drug classes, including the possession of low level resistance to penicillins. Subsequently, the isolate was subjected to capsular serotyping and was identified as serotype 19F. The clinical improvement of the patient is unknown as he did not come back for follow-up. As the isolate was found to be susceptible to the empiric antibiotic levofloxacin, a clinical recovery is presumed.

Fig. 1: Antibiotic susceptibility testing of the multidrug resistant *S. pneumoniae* isolate showing no zone of inhibition around the discs oxacillin (OX), erythromycin (E) and cotrimoxazole (COT) and wide zones of inhibition around the discs ceftriaxone (CTR) and levofloxacin (LE). >14 mm zone of inhibition around the optochin (Op) disc enables the identification of the organism.

Table 1: Minimum inhibitory concentrations of the common antibiotics for the reported isolate

Antibiotic	MIC (µg/ml)	Interpretation
Penicillin	4	Intermediate
Ceftriaxone	1	Susceptible
Erythromycin	8	Resistant
Clindamycin	1	Resistant
Tetracycline	16	Resistant
Sulfamethoxazole-Trimethoprim	320	Resistant
Levofloxacin	0.5	Susceptible
Linezolid	2	Susceptible
Vancomycin	0.5	Susceptible

DISCUSSION

The clinical manifestations of *S. pneumoniae* can vary from asymptomatic colonization of the upper respiratory tract to severe systemic infections such as pneumonia, septicaemia and meningitis. Asymptomatic nasopharngeal carriage is a common phenomenon occurring in 20 - 70% of the general population, especially in children [4]. During nasopharyngeal colonization, *S. pneumoniae* can undergo genetic exchange by transformation resulting in the acquisition of antibiotic resistance determinants. Prolonged asymptomatic carriage also increases the chance of exposure to antibiotics administered for other unrelated conditions, resulting in the selection of the drug resistant strains [5].

Resistance to penicillin was the earliest to be observed. Penicillin and other β-lactam antibiotics exert their bactericidal action on *S. pneumoniae* by binding to any of the six known penicillin binding proteins (PBPs) namely 1A, 1B, 2A, 2B, 2X, and 3. Uptake of genetic elements by transformation may alter one or more PBPs reducing their affinity for β-lactams [6]. Alterations in PBP2X and PBP2B result in low level resistance to penicillin which can be overcome usually by treating with higher β-lactams like cephalosporins. The reported isolate being resistant to oxacillin and susceptible to cephalosporin implies the possession of low level penicillin resistance. High level resistance to penicillin can be conferred by cumulative mutations of the other

PBPs over the initial mutations in PBP2X and 2B. Strains with high level penicillin resistance are resistant to all of the currently available β-lactams and require other classes of drugs for treatment [7]. Although isolated resistance to penicillin is found to be very high in most of the Asian countries and some in the western world, it is comparatively much lower in India [2].

Resistance to macrolides can occur commonly due to mutations in the ermB gene causing modifications of RNA binding site. ermB mutations also confer resistance to other antimicrobials acting on the RNA including other macrolides, lincosamides and streptogramin-B. The other mechanism for macrolide resistance is the mutations of the mefA or mefE genes which lead to increased efflux of the antibiotic before it reaches its site of action.(8) The frequency of isolated resistance to macrolides is very high in most of the Asian countries but still low in India [2].

Resistance to cotrimoxazole is rapidly acquired by point mutations in the genes encoding for enzymes of the folate synthesis pathway [9]. The prevalence of cotrimoxazole resistant strains of *S. pneumoniae* is much higher in India, accounting to around 70 to 80%. The probable reason for the increased cotrimoxazole resistance might be due to its frequent use in the treatment of upper respiratory tract infections as recommended by the World Health Organization (WHO) [3].

An isolate of *S. pneumoniae* is said to be multi drug resistant if it is resistant to at least three antibiotics of different drug groups [8]. The first MDR-SP was reported from South Africa in 1977 and its incidence has always been on the rise [10]. Recent multi-centric reports indicate the prevalence of MDR-SP to be around 40% in western countries and nearly 60% in the Asian countries [2, 8]. Lalitha MK *et al*. reported a MDR-SP from India [11]. Since then, the incidence in the country was almost nil for over a decade probably due to the inadequacy in detection of *S. pneumoniae* by most diagnostic laboratories. The incidence was reported to be only 4% in 2010 while it was found to be as high as 20% in 2013 [3, 12].

Based on the differences in the capsular polysaccharide, *S. pneumoniae* is divided into 94 serotypes. Pneumococcal serotyping can be performed by the Quellung reaction or by co-agglutination and has a good degree of correlation with the pathogenic potential, geographical distribution and antimicrobial resistance. Among the 94 known serotypes, only a few such as 1, 4, 5, 7F, 8, 12F, 14, 18C, and 19A are commonly implicated in invasive disease. Serotypes 1 and 19A cause pneumonia with subsequent haematogenous dissemination leading to meningitis or septicaemia if untreated. Meningitis due to Serotype 1 is more prevalent in the Africa and has a high fatality rate. Serotype 14 commonly causes pneumonia in adults which usually does not progress haematogenic dissemination. Serotypes 1, 3, and 19A are likely to cause empyema and hemolytic uremic syndrome [13]. The reported serotype 19F has caused pneumonia. With the advent of the seven valent pneumococcal conjugate vaccine (PCV7), invasive peumococcal disease with the vaccine serotypes 4, 6B, 9V, 14, 18C, 19F and 23F has significantly reduced. However, infections due to non-vaccine serotypes such as 19A is currently on the rise [8].

The most prevalent serotypes in India are 1, 5, 19F, 6B, 14, and 3 in the decreasing order of frequency and the reported isolate belonging to serotype 19F corresponds to this pattern of occurrence. The serotype prevalence in the South-East Asian countries also resembles the Indian scenario with a ranking order of 19F, 23F, 14, 6B, 1, and 3. In contrast, the serotype prevalence in the developed countries of the west is significantly different with 9V, 4, 7F and 12F being the common serotypes [14]. MDR-SP strains belong predominantly to the serotypes 6, 9, 14 and 23 [12]. In the countries advocating vaccination with PCV7, the MDR-SP strains of non-vaccine serotype 19A is increasing in prevalence [15]. As widespread pneumococcal vaccination is not being carried out in the region from where this case is reported, the occurrence of serotype 19F is expected.

Until recently, MDR-SP has only been a problem in a few developed nations and most of the Asian countries except India. However, recent reports indicate a sudden alarming rise of MDR-SP in India with the current prevalence comparable to the countries of the West [12]. This resistance trend in pneumococcus is a reason to worry in India, as it may rule out the use of the cost effective cotrimoxazole in the community setting. Although many countries have reported a steep drop in invasive pneumococcal disease following vaccination, it can result in replacement phenomenon with non-vaccine serotypes. However, effective reduction of the MDR-SP strains can be achieved for the time being if widespread vaccination is initiated across the country. This should be complemented with a suitable national antibiotic policy addressing the role of MDR-SP in community acquired pneumonia.

CONCLUSION

To the best of our knowledge, this is the first report of MDR-SP from the southernmost part of India and might probably represent only the tip of the iceberg. Although the patient had no history of international travel, the possibility of dissemination of imported strains of MDR-SP from geographically adjacent countries has to be ruled out with further phylogenetic studies. If necessary preventive strategies are not employed promptly, it would only be a matter of time when the prevalence of MDR-SP in India shoots to greater heights.

REFERENCES

1. Wardlaw T, Johansson EW, Hodge M; Pneumonia: The forgotten killer of children. WHO Press, Geneva, 2006.
2. Kim SH, Song J-H, Chung DR, Thamlikitkul V, Yang Y, Wang H *et al*.; Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. Antimicrob Agents Chemother., 2012; 56(3): 1418–1426.
3. Kumar KLR, Ganaie F, Ashok V; Circulating serotypes and trends in antibiotic resistance of invasive *Streptococcus pneumoniae* from children under five in Bangalore. J Clin Diagn Res., 2013; 7(12): 2716–2720.
4. García-Rodríguez JA, Fresnadillo Martínez MJ; Dynamics of nasopharyngeal colonization by potential respiratory pathogens. J Antimicrob Chemother., 2002; 50 (Suppl S2): 59–73.
5. Marks LR, Reddinger RM, Hakansson AP; High levels of genetic recombination during nasopharyngeal carriage and biofilm formation in *Streptococcus pneumoniae*. MBio., 2012; 3(5): pii: e00200-12.
6. Muñoz R, Dowson CG, Daniels M, Coffey TJ, Martin C, Hakenbeck R *et al*.; Genetics of resistance to third-generation cephalosporins in clinical isolates of *Streptococcus pneumoniae*. Mol Microbiol., 1992; 6(17): 2461–2465.
7. File TM Jr., Jacobs MR, Poole MD, Wynne B, 546, 547, 548, 549, 550, 551, 556, 557 and 592 Clinical Study Groups; Outcome of treatment of respiratory tract infections due to *Streptococcus pneumoniae*, including drug-resistant strains, with pharmacokinetically enhanced amoxycillin/clavulanate. Int J Antimicrob Agents, 2002; 20(4): 235–247.
8. Reinert RR; The antimicrobial resistance profile of *Streptococcus pneumoniae*. Clin Microbiol Infect., 2009; 15 (Suppl 3): 7–11.
9. Maskell JP, Sefton AM, Hall LM; Multiple mutations modulate the function of dihydrofolate reductase in trimethoprim-resistant *Streptococcus pneumoniae*. Antimicrob Agents Chemother., 2001; 45(4):1104–1108.
10. Jacobs MR, Koornhof HJ, Robins-Browne RM, Stevenson CM, Vermaak ZA, Freiman I *et al*.; Emergence of multiply resistant pneumococci. N Engl J Med., 1978; 299(14): 735–740.
11. Lalitha MK, Pai R, Manoharan A, Appelbaum PC, CMCH Pneumococcal Study Group; Multidrug-resistant *Streptococcus pneumoniae* from India. Lancet, 2002; 359(9304): 445.
12. Chawla K, Gurung B, Mukhopadhyay C, Bairy I; Reporting emerging resistance of *Streptococcus pneumoniae* from India. J Glob Infect Dis., 2010; 2(1): 10–14.
13. Song JY, Nahm MH, Moseley MA; Clinical implications of pneumococcal serotypes: invasive disease potential, clinical presentations, and antibiotic resistance. J Korean Med Sci., 2013; 28(1): 4–15.
14. Molander V, Elisson C, Balaji V, Backhaus E, John J, Vargheese R *et al*.; Invasive pneumococcal infections in Vellore, India: clinical characteristics and distribution of serotypes. BMC Infect Dis., 2013; 13: 532.
15. Song J-H; Advances in pneumococcal antibiotic resistance. Expert Rev Respir Med., 2013; 7(5): 491–498.