Malaysian Journal of Medicine and Health Sciences Vol. 1(1) January 2007: 79–83

Case Study

Penicillin Resistant *Streptococcus pneumoniae*

MZA Hamid, TH Ting & O Norlijah

Department of Paediatrics, Faculty of Medicine and Health Sciences
Universiti Putra Malaysia, 43400UPM, Serdang, Selangor, Malaysia

ABSTRACT

Antibiotic resistance is uncommon in paediatric community acquired pneumonia (CAP) in Malaysia. However, with the increased use of antibiotics, there is a risk of penicillin-resistant *Streptococcus pneumoniae* (PRSP) pneumonia which results in antibiotic treatment failure. We report here a case of CAP complicated by empyema, caused by PRSP, which presented as acute respiratory distress in a 19-month-old boy.

Keywords: Penicillin, *Streptococcus pneumoniae*, pneumonia

INTRODUCTION

Pneumonia is a lower respiratory tract infection caused by a variety of bacteria namely *Streptococcus*, *Staphylococcus*, *Pseudomonas, Haemophilus, Chlamydia and Mycoplasma* groups. Amongst children, community acquired pneumonia (CAP) is due to *Streptococcus pneumoniae* which is known to cause a high incidence of mortality and morbidity worldwide.[1,2,3] Apart from pneumonia, this bacteria is also known to cause life-threatening conditions such as meningitis and bactaeremia. [2,3,4] Naturally responsive to antibiotic treatments, the last three decades have seen the emergence of a new strain of *S. pneumoniae* which is increasingly resistant to penicillin. [5] Thus, there have been increasing reports of CAP caused by these new strains which were resistant not only to penicillin but to multiple antibiotics as well. [6,7] Following this development, the National Committee for Clinical Laboratory Standards USA has currently categorised pneumococcal isolates as penicillin susceptible if the minimum inhibitory concentration (MIC) is less than 0.06 μg/ml, of intermediate susceptibility if MIC is 0.1 to 1.0 μg/ml and resistant if MIC is greater than 2.0 μg/ml. [8] We report a case of CAP caused by PRSP presenting as respiratory distress.

CASE REPORT

The case involved a 19-month-old Malay boy who was first seen in the ward with a four-day history of fever, cough and increasing shortness of breath. The patient was also lethargic and not feeding well. He gave no history of receiving antibiotics from private practitioners prior to this admission.

On examination, he appeared ill, drowsy and dyspnoeic. He had a temperature of 39°C, respiratory rate of 60 breaths/min, pulse of 170 beats/min and blood pressure of 97/64 mmHg. Oxygen saturation on high flow mask was 100%. On auscultation of the lungs, bronchial breath sounds and decreased air entry was noted on the left lung basally. Blood

Corresponding author: *zaini@medic.upm.edu.my*

investigations showed a high leucocyte count of 24.0 x 10^9 / l, low haemoglobin level of 9.1 g/dl and normal renal profile. An arterial blood gas sample, taken on 100% oxygen, showed compensated metabolic acidosis. The patient was then transferred to the intensive care unit and subsequently intubated.

Blood and tracheal aspirated cultures were obtained before he was started on a high dose of intravenous penicillin and cefotaxime. Fluid replacement therapy and vasopressors were then started as his blood pressure was low. Two days after admission, the blood culture grew *S. pneumoniae*, which was resistant to penicillin, but sensitive to erythromycin, tetracycline and vancomycin. The MIC to penicillin on the disc susceptibility testing was 3 μg/ml. Hence, the antibiotics were changed to intravenous vancomycin and ceftriaxone.

Over the next four days his condition progressively improved with resolution of fever and improvement in the other respiratory signs. Serial blood cultures remained negative for two weeks and he was discharged well. On the next follow-up visit, he remained very well. A repeated chest radiograph on follow-up was normal.

DISCUSSION

S. pneumoniae remains the leading cause of CAP among children worldwide, with the highest incidence occurring in infants less than two years old.[9] Over-use of antibiotics has resulted in the emergence of penicillin-resistant isolates which complicates the current management of CAP among children.[10,11] Heath *et al.*[14] found that the prevalence across Europe in a decreasing order was as follows: Spain (51.0%) followed by Hungary (57.8%), and lowest in more developed countries namely Germany (1%) and Netherlands (2%). Prevalence was also noted to be significantly higher in other parts of the world such as in South Africa which reported 62.2% cases of penicillin-resistant CAP[12] and approximately 70% in a population studied in South Korea. [13] The Asian Network for Surveillance of Resistant Pathogens (ANSORP) documented that in Malaysia there was an increase in incidence of nearly four-fold (10% in 1996 and 43% in 2003) of penicillin–resistant pneumococcal pneumonia. [12]

By design, *S. pneumoniae* has the ability to transform its genetic make-up after being exposed to antibiotics particularly penicillin. Experts generally believe that the resistance to antibiotics may involve one or probably both of these mechanisms - either the blockage of *S. pneumoniae* replication or the binding of one or more enzymes required for cell wall synthesis, which eventually results in mutations in the penicillin-binding proteins (PBP) of the bacterial make-up.[14] The degree of the mutations is highest in the most resistant *S. pneumoniae*. Since many of the beta-lactam antibiotics share similar binding properties as penicillin, the mutated penicillin-resistant strains may show diminished sensitivities to other beta-lactam antibiotics as well. This might explain why there is resistance not only to penicillin but to other related antibiotics as well, especially the first and second generation cephalosporins. [15] It is, however, almost certain that the third-generation cephalosporins are still effective against penicillin-resistant strains mainly due to the fact that the newer generation cephalosporins have higher levels of tissue penetration and are thus effective against the mutated *S. pneumoniae*. [15]

Many clinicians assume that PRSP would respond poorly to antibiotic therapy, given the fact that PRSP itself is due to antibiotic resistance. However, several studies seem to

refute this fact. In the USA, three studies have addressed the response of PRSP to antibiotic treatment. They concluded that patients with both intermediate and high-level resistant PRSP treated with other antibiotics performed no differently from those receiving penicillin alone. However, these results need to be treated with caution as all the studies were observational or retrospective rather than randomised controlled trials, hence the results reported could be one-sided.[14] Mortality rates due to PRSP strains and non-PRSP strains showed no significant difference as reported by Shelley *et al.*[16]

Due to the complexity of the PRSP, one would expect that pneumococcal pneumonia warrants alternative and expensive antibiotics. However, as the above evidence suggests, penicillin or earlier generation cephalosporin group antibiotics appear to be adequate in treating susceptible or intermediate resistant SP. Clinicians should reserve the use of third-generation cephalosporins and vancomycin only for cases which are definitely pneumococcal resistant (MIC > 2.0 μg/ml) as in our case.[14] Among those susceptible to PRSP are children from countries with a high prevalence of antibiotic resistance, patients with immuno-deficiency, previous history of multiple antibiotic treatment and children not responding to conventional antibiotic therapy.[14]

Among identifiable risk factors associated with PRSP is the previous use of antibiotics in children infected with pneumococcal pneumonia.[17] Studies have documented that the use of either penicillin or ampicillin three months prior to *S. pneumoniae* infection may increase the risk of PRSP[18,19,20] although this was not so in our case as our patient did not receive any antibiotic therapy prior to his illness. It was also reported that those with private medical coverage were at greater risk of developing PRSP than those with state or no medical coverage. One possible explanation is that those in a position to receive private medical coverage may have received more antibiotic exposure. Given the fact that this country has no control on 'over the counter' purchase of common antibiotics, it is also postulated that families from higher income groups may have greater access to antibiotics for common illnesses even without prescription hence increasing the risk of developing PRSP.

The emergence of these PRSP strains has made management of these cases more difficult. This highlights the importance of possible prevention by vaccination coverage in these vulnerable children. Previous studies have showed that the majority of serotypes isolated in Asia, particularly in Malaysia belong to serotypes 1, 4, 6A, 6B, 14, 19B, 19F and 23F.[3,20,21] The newly developed seven-valent conjugated vaccine, made up of these serotypes, offers the prospect of preventing major pneumococcal illnesses in children. It is hoped in the near future that introduction of this vaccine will provide a preventive coverage to these vulnerable children. Nonetheless, at present it is imperative for all clinicians to be made aware of PRSP pneumonia and how best to identify and manage it effectively.

REFERENCES

[1] Reichler MR, Allphin AA, Breiman RF *et al.* The spread of multiple resistant *Streptococcal pneumoniae* at a day care center in Ohio. J Infect Dis 1992; 166 (6): 1346-53

[2] Breiman RF, Butler JC, Tenover FC *et al.* Emergence of drug-resistant pneumococcal infections in the United States. JAMA 1994; 271 (23): 1831-5.

[3] Jamal F, Pit S, Isahak I *et al.* Pneumococcal infection in hospitalized patients: a four-year study in Malaysia. Southeast Asian J Trop Med Public Health 1987; 18 (1): 79-84.

[4] Appelbaum PC. Epidemiology and *in vitro* susceptibility of drug-resistant *Streptococcus pneumoniae*. Pediatr Infect Dis J 1996; 15 (10): 932-4.

[5] Bartlett JG, Breiman RF, Mandell LA *et al.* Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. Clin Infect Dis 1998; 26 (4): 811-38.

[6] Hofmann J, Cetron MS, Farley MM *et al.* The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. N Engl J Med 1995; 333 (8): 481-6.

[7] Pallares R, Linares J, Vadillo M *et al.* Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N Engl J Med 1995; 333 (8): 474-80.

[8] National Committee for Clinical Laboratory Standard, Performance Standards for Antimicrobial Susceptibility Testing, NCCLS document M 100S8) Villanova, Pennsylvania, National Committee for Clinical Laboratory Standard 1998; Vol 18.

[9] Garcia-Leoni ME, Cercenado E, Rodeno P *et al.* Suceptibility of *Streptococcus pneumoniae* to penicillin: a prospective microbiological and clinical study. Clin Infect Dis 1992; 14 (2): 427-35.

[10] McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA 1995; 273 (3): 214-9.

[11] Jernigan DB, Cetron MS, Breiman RF *et al.* Minimizing the impact of drug-resistant *Streptococcus pneumoniae* (DRSP). A strategy from DRSP Working Group. JAMA 1996; 275 (3): 206-9.

[12] Jacobs MR, Koornhof HJ, Robins-Browne RM *et al.* Emergence of multiply resistant pneumococci. N Engl J Med 1978; 229 (14): 735-40.

[13] Lee HJ, Park JY, Jang SH *et al.* High incidence of resistance to multiple antimicrobials in clinical isolates of *Streptococcus pneumoniae* from a university hospital in Korea. Clin Infect Dis 1995; 20 (4): 826-35.

[14] Heath PT, Breathnach AS. Treatment of infections due to resistant organisms. Br Med Bull 2002; 61: 231-45.

[15] Fraimow HS, Abrutyn E. Pathogens resistant to antimicrobial agents. Epidemiological, molecular mechanisms, and clinical management. Infect Dis Cli North Am 1995; 9 (3): 497-530.

[16] Deeks SL, Palacio R, Ruvinsky R *et al.* Risk factors and course of illness among children with invasive penicillin-resistant *Streptococcus pneumoniae.* The *Streptococcus pneumoniae* Working Group. Pediatrics 1999; 103 (2): 409-13.

[17] Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. Microb Drug Resist 1997; 3 (2): 117-23.

[18] Friedland IR. Comparison of the response to antimicrobial therapy of penicillin-resistant and penicillin-susceptible pneumococcal disease. Pediatr Infect Dis J 1995; 14 (10) : 885-90.

[19] Bedos JP, Chevret S, Chastang C *et al.* Epidemiological features of and risk factors for infection by *Streptococcus pneumoniae* strains with diminished susceptibility to penicillin: findings of a French survey. Clin Infect Dis 1996; 22 (1): 63-72.

[20] Song JH, Jung SI, Ko KS, Jamal F *et al.* High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP Study). Antimicrob Agents Chemother 2004: 48 (6); 2101-7.

[21] Rohani MY, Raudzah A *et al.* Epidermiology of *Streptococcus pneumoniae* infection in Malaysia. Epidemiology. Infect 1999; 122: 77-83