PENICILLIN-RESISTANT STREPTOCOCCUS PNEUMONIAE – A REVIEW

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Since the first report in 1967, the incidence of Penicillin Resistant Streptococcus pneumoniae (Pneumococcus) has risen steadily worldwide, and now complicates diagnostic and treatment strategies for infections due to this organism. More worrisome is the fact that in areas where Penicillin Resistant Streptococcus pneumoniae (PRSP) has become established, resistance to other antimicrobial agents such as cephalosporins, sulphonamides and macrolides is also common. This development has a grave implication for therapy of life threatening pneumococcal infections like meningitis and septicaemia, with the extended spectrum cephalosporins, such as ceftriaxone and cefotaxime, and the newer macrolides, azithromycin and clarithromycin. The mechanism of resistance to β-lactam antibiotics is decreased binding of drug to the bacteria cell wall brought about by genetic transformation in bacterial chromosome. Recently, using molecular techniques that can index overall relatedness of the drug resistant pneumococcal isolates, it has been possible to establish clonal dissemination of drug resistant pneumococci across continents, with acquisition of additional drug resistance determinants as a result of "local" antibiotic selective pressures. This is a review of literature on the epidemiology, mechanism of resistance, laboratory identification, treatment, prevention and control of Penicillin Resistant Pneumococci (PRP), with emphasis on the problems of identification and reporting in developing countries.

Key words: penicillin, Streptococcus pneumoniae, resistant, extended spectrum cephalosporins.

INTRODUCTION

Streptococcus pneumoniae infections are among the leading causes worldwide of illness and death in young children, persons with underlying illness, and the elderly. In the United States of America alone, Streptococcus pneumoniae is a leading cause of morbidity and mortality, resulting each year in an estimated 3,000 cases of meningitis, 50,000 cases of bacteraemia, 500,000 cases of pneumonia and 7,000,000 cases of otitis media (1, 2). In developing countries, 50% of the estimated 4 million child deaths annually from
pneumonia are caused by *Streptococcus pneumoniae* (3).

In the past, *Streptococcus pneumoniae* was almost uniformly susceptible to penicillin, allowing most physicians to treat persons who had severe infections with penicillin alone and without testing for resistance. Since the 1960s however, resistance to penicillin and most other antimicrobial agents, has spread rapidly. Penicillin Resistant *Streptococcus pneumoniae* (PRSP) was first reported in 1967 in Australia (4), in New Guinea in 1969 (5) and in South Africa in 1977 (6), and since then in many countries throughout Africa, America, Asia and Europe (7-26).

In Africa, with the exception of South Africa, literature on the occurrence of PRSP appears sparse. The few reports have documented low prevalence rate, which is probably due to gross underreporting. Poor or absent antibiotic resistance surveillance and infection control programmes, and poor laboratory backup in many health institutions are some of the factors responsible for underreporting of the occurrence of PRSP and other resistant organisms in these countries. This article reviewed the epidemiology, diagnostic and therapeutic difficulties, and preventive measures for PRSP and emphasizes the need to increase surveillance for these organisms in developing countries.

**HISTORICAL/Epidemiological Perspectives**

The German pathologist, Klebs in 1875 described *Streptococcus pneumoniae* in the fluid from the lungs of a man dying with pneumonia (27). In 1881, the organism was concurrently identified in the old and new worlds, by Pasteur in France, who named it *Microbe Septicemique du Salive*, and Sternberg in the United States, who called it *Micrococcus pasteurii* (27,28). By late 1880s, the term pneumococcus was generally used because this bacterium has come to be recognized as the most common cause of lobar pneumonia (28). It was also recovered from several body sites such as cerebrospinal fluids, synovial fluids, kidney, middle ear, blood and the pericardium (27,28).

In 1890s, Felix and klumper showed that immunization
with killed pneumococci protected animals against subsequent pneumococcal challenge, and further, that protection could be transferred by infusing serum from immunized mice into naive recipients (29). Felton prepared the first purified pneumococcal capsular polysaccharides for immunization of human subjects (30), and a preparation of type 1 polysaccharide was used to abort an epidemic of pneumonia at a State Hospital in Worcester, Massachusetts in 1938 (31). MacLeod and coworkers further confirmed this during the World War II when they found that vaccinating military recruits with capsular material from several serotypes of Streptococcus pneumoniae greatly reduced the incidence of pneumonia due to serotypes present in the vaccine, but not other pneumococcal serotypes (32). Serotypes of pneumococci were earlier recognized, based on the observation that injection of killed organism into a rabbit stimulated the production of antibody that agglutinated and caused capsular swelling of the immunizing strains, as well as of some, but not all, other pneumococcal isolates (29). Capsule swelling (Quellung) reaction became the basis of the American and Danish serotyping schemes of *Streptococcus pneumoniae*.

The name Diplococcus was adopted in 1926 based on the presence of paired cocci on Gram stained sputum. In 1974 it was renamed *Streptococcus pneumoniae* based on the presence of chains when grown in liquid medium (27). *Streptococcus pneumoniae* was the subject of pioneering genetic research work by Griffith (33), when in 1928, he demonstrated genetic transformation in *Streptococcus pneumoniae*. In the 1930s, it was recognized that a large proportion of healthy population carried pneumococci in the nasopharynx and that this was often a source of disease in contacts of these asymptomatic carriers (28,34).

In the pre-antibiotic era, mortality from untreated pneumococcal disease was 77% (35). It was 50% in patients treated with specific antipneumococcal serum (35). Following the introduction of sulphonamides in 1930 and penicillin in 1945, mortality decreased to about 25% (36) but remained unchanged at this rate for about three decades of antibiotic therapy (37,38,39).
During this period (1940s to 1970s) however, occasional strains of pneumococcus exhibiting increased resistance to penicillin (4,40), tetracycline (41,42), erythromycin and lincomycin (43,44) had emerged.

The first documented evidence of resistance to pneumococcus was in 1912 by Morgenroth and Kaufman (45) when optochin (ethylhydrocuprein hydrochloride) resistant pneumococci were obtained from experimentally infected mice treated with optochin. Optochin resistant pneumococci were then reported among clinical isolates obtained from patients treated with optochin in 1915 (46). Sulphonamide resistant pneumococci were reported in patients with meningitis and lobar pneumonia between 1939 and 1943 (47). Penicillin resistance was first described in 1945 among mutant strains of pneumococci in vitro (40) shortly after the introduction of penicillin into the market. Clinical isolates of Streptococcus pneumoniae with reduced susceptibility to penicillin were first reported in Boston in 1965 (48). Penicillin minimum inhibitory concentration (MIC) of 0.1 and 0.2 μg/mL were reported in two of the two hundred isolates tested. Despite these findings, the investigators failed to recognize the clinical significance of their discovery. The first pneumococcal strain with reduced susceptibility to penicillin (MIC 0.6 μg/mL), for which clinical relevance was recognized, was reported in 1967 (4) after being isolated from a 25-year old Australian woman. During the next decade, several alarming reports were published documenting worldwide spread of pneumococci with reduced susceptibility to penicillin (MIC 0.1 – 1 μg/mL). (5-9). In 1977 (10), pneumococci exhibiting high level penicillin resistance (MIC ≥ 2.0 μg/mL) were isolated from young African children admitted to King Edward VIII Hospital, Durban, South Africa, with meningitis, septicaemia, otitis media, pneumonia and empyema. By the early 1980s, worldwide distribution of multidrug resistant pneumococci have been described with reports from New Guinea, Israel, Poland, South Africa and the United States of America (11-15).

The incidence and pattern of penicillin resistance among pneumococci remained fairly stable in the early 1980s (14), but due to the various degree of resistance en-
countered and the various nomenclatures used, the Centre for Disease Control and Prevention (CDC), in 1995 suggested a standardized classification of resistance level (49). CDC defines susceptibility of *Streptococcus pneumoniae* to Penicillin as MIC $\leq 0.06$ µg/mL. All isolates for which the MIC is $\geq 0.1$ µg/mL are regarded as non-susceptible. Isolates that are non-susceptible are characterized further as Penicillin intermediate (*Peni*; MIC 0.1-1 µg/mL) or Penicillin resistant (*Penr*; MIC $\geq 2.0$ µg/mL). Isolates for which MIC is $\geq 2.0$ µg/mL were previously referred to as displaying high-level penicillin resistance (50). This terminology is no longer advocated by CDC (49).

Between 1979 and 1987, non-susceptible pneumococci accounted for approximately 5% of the strains recovered in the United States. During the same period, Penicillin resistant strains (*Penr*) were rare, approximately 0.02% (1 of 4585) of pneumococci sterile-site isolates submitted to the CDC Sentinel Hospital Surveillance system (51). By the early 1990s, however, a dramatic increase in the frequency of isolation of non-susceptible pneumococci was reported (52-57), with a corresponding increase in Penicillin resistant (*Penr*) strains. For example in 1991 - 1992, 2.6% of all isolates were Penicillin resistant as against 7.3% in 1992-93 (52, 53) and 9.5% in 1994-95 (57). Similarly, several other countries reported increasing incidence of Penicillin non-susceptible strains with corresponding increase in Penicillin resistant (*Penr*) strains during this period (16-26). The common serotypes of pneumococci resistant to penicillin (MIC $\geq 2.0$ µg/mL) and other β-lactam agents encountered include serotypes 6A, 6B, 19A, 19F, 14 and 23 (13). Others include serotypes 1, 3, 5, 15, 31 and 35 (15). In the United States, outbreaks in daycare centres were caused mainly by serotypes 6B, 14, 19F and 23 (58, 59).

In Africa, only few surveys have been reported except in South Africa, where resistant rates are close to 20% (60). Surveys carried out in Nairobi, Kenya in 1981 (61) and during 1991 to 1992 (62) gave 26% prevalence rates. In Tunisia, a rate of 10% was reported (63). Reports from Zambia (64), Senegal and Ivory Coast (63) have posted...
rates below 5% and less than 2% in Morocco and Egypt (63). A survey in Nigeria in 1978 reported a 20% prevalence rate for Penicillin Resistant Pneumococci (65). The relatively few surveys carried out by African countries do not give a true picture of the occurrence of PRSP in this continent. More surveys will be necessary to know the true prevalence in these countries.

Penicillin Resistant Pneumococci have been recovered more frequently from children five years or younger than from other age group (1, 2, 9-13,64,67,68,73,74). Although young children are still at risk for resistant infection, an increased frequency of drug resistant pneumococci has been encountered in adults (60). Risk factors for an infection secondary to a resistant pneumococcal strain include hospitalization, prior exposure to antimicrobial agents, underlying illness and tobacco use (6-13,15,19,23,39,67,68,69,71).

In areas where PRSP has been established, resistance to other antimicrobials, such as cephalosporins (67-71), sulphonamides (15, 60, 73) and macrolides (66, 74) is also common. The identity of drug-resistant isolates within a country or in different countries has been investigated using techniques such as polymerase chain reaction (BOX PCR), pulse field gel electrophoresis (PFGE), multilocus enzyme electrophoresis (MLEE), penicillin binding protein (PBP) profiling and multilocus sequence typing (MLST) to index their overall relatedness (75, 76). This has illustrated the extreme diversity of drug resistant pneumococci particularly in countries such as Spain and Africa, where resistant isolates have emerged rather than being imported. However, superimposed on this diversity is the emergence and clonal spread of resistant isolates that are presumably fitter than other isolates. Thus in Spain although there is a great divergence in the relatedness of resistant isolates, more than 60% of all Penicillin resistant isolates belong to four major clones; Spain$^{23F}$-1, Spain$^{68}$-2, Spain$^{9V}$-3 and Spain$^{14}$-5 (77). Two of these clones have been extensively studied. The first major clone, Spain$^{23F}$-1 (resistant to penicillin, tetracycline, chloramphenicol and sometimes erythromycin) probably arose from Spain in the early 1980s and since then has spread across more than six other
countries in three continents (78). The spread of this clone has been accompanied by the emergence of variants that have acquired additional drug resistance determinants as a result of "local" antibiotic selective pressures. The second major Spanish clone, SpainAB-2 is also resistant to penicillin, tetracycline and chloramphenicol and has become prevalent in Iceland and the United Kingdom (79), other European countries (80,81) and in Asia (82). Extensive human population mobility is the major factor in the global dissemination of these resistant clones.

MECHANISM OF RESISTANCE IN PRSP

Pneumococcal resistance to β-lactam agents, like Penicillins and Cephalosporins, is due to changes in the target sites of the enzymes called Penicillin Binding Proteins (PBP). These high molecular weight proteins are believed to catalyze the terminal stages in peptidoglycan (murein) synthesis (83). There are six PBPs found in susceptible strains of Streptococcus pneumoniae: PBP 1a, 1b, 2a, 2x, 2b and 3 (84). All are high molecular weight proteins except PBP3, which is probably not too involved in β-lactam mediated cell lysis (84, 85). β-lactam compounds inhibit these enzymes by covalently binding to their active sites (84).

The altered PBPs in pneumococcus have low affinity for penicillin and related β-lactam compounds (85), a mechanism which only occurs in organisms that are naturally transformable. Altered PBPs also play a role is resistance to Penicillin in other naturally non-transformable strains like Staphylococcus aureus and enterococci (86), but in these cases, it is due to acquisition of new abnormal PBPs, rather than decrease in the affinity of the normal PBPs. Pneumococcal isolates with high Penicillin MIC seems to be entirely due to the expression of low affinity forms of PBP 1a, 2a, 2b, 2x and perhaps 1b (87). There is a reduction in the affinity of at least three of these five PBPs. For example, resistance to at least 8 μg/mL can be achieved by alterations in only PBP 1a, PBP 2x and PBP 2b. Since PBPs in these strains also have decreased affinities for other β-lactam antibiotics, most PRSP have increased resistance to third generation cephalosporins including ceftriaxone and cefotaxime. High-level resistance
to cephalosporins requires reduction in the affinities of only PBP 2x and PBP 1.

The reduction in the affinity of PBPs for β-lactam compounds results from the appearance of the so-called "mosaic" amino acid sequences of the proteins (85). Over the last few decades, the high selective pressures provided by antibiotics in the environment of the bacteria have selected for strains that have these new or changed PBPs, less able to bind β-lactam antibiotics. What we see today are pneumococci that have PBP encoding chromosomal genes that are hybrid molecules made with DNA from *Streptococcus mitis* and other yet to be identified streptococcal species (88). Many different "mosaic" genes have been sequenced to date. It is difficult to calculate the exact events that gave rise to these variants PBPs. To complicate matter is the fact that these "mosaic" genes have been transferred to other viridians streptococci such as *Streptococcus sanguis* and *Streptococcus oralis* (87). As a result of the gene flow between these naturally transformable streptococci, it is difficult to determine the events that occurred to produce these mosaic PBPs now found in resistant pneumococci.

PRSP with MIC ≥ 2 µg/mL are also more likely to be resistant to non β-lactam agents such as chloramphenicol, trimethoprim-sulphamethoxazole, erythromycin, tetracycline and aminoglycosides (15,60,66,74,75). Resistance to chloramphenicol, tetracycline and erythromycin appears to be chromosomally mediated (89). A 7.244 kb defective transposon Tn 1207.1 containing *mef* (A) gene has been found inserted in the competence cel B chromosomal region of *Streptococcus pneumoniae* conferring resistance to macrolide (M phenotype) via an active efflux mechanism (90). Another 25.3 kb conjugative transposon, Tn 1545 has also been found inserted into the chromosome of resistant pneumococcus (91). This transposon carries the *erm* (B) gene that confers resistance to erythromycin and the structurally unrelated macrolide, lincomamide and streptogramin B (MLS_b phenotype), through methylation of 23S rRNA, the common target of these agents. This transposon also carries the *tet* (M) gene.
that codes for tetracycline resistance via the production of a protein that binds to the ribosome and blocks protein synthesis (92). Resistance to trimethoprim-sulphamethoxazole is attributed to trimethoprim and occurs by a decrease in the affinity of trimethoprim for its target enzyme, dihydrofolate reductase (93). Chloramphenicol resistance is due to the production of an inducible chloramphenicol acetyltransferase (94).

It appears that pneumococci, in addition to having incorporated DNA from non-pneumococcal streptococci, may have also shared DNA with Gram-negative microbes in other to acquire additional drug resistance. The genes that encode resistance to erythromycin, tetracycline and aminoglycosides, *erm* (B), *tet* (M) and *aph* (A3) respectively, identified in PRSP have also been found in *Escherichia coli* and *Klebsiella spp*, *tet* (M) in resistant *Haemophilus* and *Neisseria spp*, and *aph* (A3) in *Staphylococcus aureus*, *Enterococcus faecalis* and *Helicobacter spp* (89).

Although the quinolone antimicrobials have improved spectrum of activity against Gram-positive organisms, they do not possess sufficient activity to be clinically useful against *Streptococcus pneumoniae*. One of the genes responsible for resistance to quinolones is *gyr* (A), which encodes the A-subunit of DNA gyrase, the site of action of quinolones (95). Newer quinolones may be potent against *Streptococcus pneumoniae* despite mutations in the *gyr* (A) and *par* (C) genes and may be useful in treating infections by this organism (96).

To date, β-lactamase producing pneumococci have not been reported. The mechanism of resistance is entirely chromosomal with horizontal transfer of resistant genes via transformation and conjugation.

**LABORATORY IDENTIFICATION OF PRSP**

*Streptococcus pneumoniae* is a fastidious organism requiring particular attention to proper laboratory procedures for identification and *in vitro* susceptibility testings (97). Routinely in the laboratory, pneumococci are identified by three reactions: the so-called alpha-haemolysis on blood agar with flat or concentrically ringed colonies, catalase negativity and solubility in bile salt or susceptibility to ethyl-
hydrocupreine (Optochin). Occasional strains may form rounded, rather than flat or concentrically ringed, colonies or may lack capsules and hence mis-identified as viridian streptococci. These atypical strains are likely to be encountered from sites with normal flora or among Penicillin resistant strains (98). Strains with zone diameter of inhibition ≥ 10 mm to optochin disk can be presumptively identified as pneumococci. Incubation in air with added CO₂ caused decreased zone size, which is reversed when pneumococci, but not viridian streptococci, are incubated in air (101). In recent years, a number of isolates have been found to be optochin resistant (102,103), which has led cautious microbiologists to rely more on the use of bile solubility for definitive identification.

IN-VITRO SUSCEPTIBILITY TESTING

Recent reports have emphasized the importance of accurate susceptibility testing of all clinically significant isolates of *Streptococcus pneumoniae*, the need for new agents, and periodic revaluation of existing drugs (1,97,104). Testing is complicated by the fact that there are currently no automated microbroth dilution MIC systems available for susceptibility testing of *Streptococcus pneumoniae*.

Laboratory may choose to use agar disk diffusion on Mueller-Hinton agar supplemented with 5% sheep blood, incubated in 5% CO₂ to screen for Penicillin resistance using the 1 µg oxacillin disk (49,97,98) or 5 µg methicillin disk (99). The cut off zone diameter of inhibition for oxacillin is 20 mm (49) and for methicillin, 25 mm (99). Oxacillin is preferred to methicillin, because of the enhanced resistance of oxacillin to degradation during storage (100). This method is also acceptable for testing other oral agents including trimethoprim/sulphamethoxazole, erythromycin, clindamycin and tetracycline as well as vancomycin for parenteral use (49,105). Penicillin disk is not used because it gives inaccurate results (98).

Susceptibility to Penicillin can be used to predict susceptibility to all other β-lactams. However, to distinguish between Penicillin intermediate and Penicillin resistant isolates, and to obtain susceptibility information for cephalosporins, a quantitative MIC test must be
done (1,49,97). The agar dilution method is regarded as the reference method for determining the MIC for pneumococcus (49,98). This is carried out in cation-adjusted Mueller Hinton agar supplemented with 5% whole defibrinated horse or sheep blood or 5% lysed and centrifuged horse blood for sulphonamides (98,106). The inoculum size is $10^4$ CFU per spot and plates are incubated in air or added 5-10% CO₂ overnight (49).

Recently, the E-test (AB Biodisk, Solna, Sweden) has become popular. This is a method of determining MIC based on diffusion of an antimicrobial gradient from a calibrated antibiotic impregnated plastic strip applied onto the surface of an inoculum coated agar plate. The antibiotic gradient produced results in an ellipse of inhibition. The point at which the ellipse meets the strip is the MIC. This technique has become widely used in clinical laboratories for quantifying MICs for penicillin and third generation cephalosporins (1,49,107). Evaluation of the E-test has shown excellent correlation with agar dilution and broth microdilution method for Penicillin G, Cefotaxime, Ceftriaxone, Amoxicillin, Chloramphenicol, Erythromycin and Tetracycline, though, the MIC for Penicillin G tends to be slightly lower resulting in some resistant strains being categorized as intermediate (107,108).

**TREATMENT OF PRSP INFECTIONS**

Opinion differs on how to treat infections caused by Penicillin Resistant Pneumococcus. There are very few randomized controlled clinical trials of antimicrobial agents for the treatment of these infections. Schreiber and Jacobs (1), in a recent review, stressed the need for more controlled trials to determine optimal antimicrobials or other intervention necessary to treat infections due to PRSP. To optimize initial or empiric therapy for pneumococcal infections, clinical health-care providers must be informed of the prevalence and patterns of resistance among isolates in their community. The degree of resistance, variability in drug levels at different sites, particularly in the CSF and middle ear, natural history of the disease at different sites and in different age groups, stage of infection at which initial or appropriate therapy was instituted and presence of underlying ill-
nesses such as malnutrition, immunodeficiency, or malignancy, are some of the factors affecting treatment outcome (15,98).

The consensus among recent reviews is that Penicillin should no longer be used in the initial treatment of pneumococcal meningitis (109-110). Several authors advocate monotherapy with third generation cephalosporin, either ceftriaxone or cefotaxime (110-112), while others suggest initial therapy should include the combination of ceftriaxone or cefotaxime with vancomycin (111,112). A clinical study by Viladrich et al in Barcelona, Spain (114) showed cefotaxime and ceftriaxone to be reasonable first agent for meningitis. Although, Penicillin was potentially effective against sensitive strains or even intermediate resistant strains in high doses, they recommended that it should not be used as first line agent in view of the poor clinical outcome in their patients. Vancomycin has also been evaluated for the treatment of PRSP associated meningitis (115), but concern about penetration into the cerebrospinal fluids in adults prompted studies of combination regimens. Vancomycin and ceftriaxone combination was found to be synergistic even against strains with high penicillin and cephalosporin MIC (116). Ceftriaxone and rifampin was also found to be effective in adults given dexamethasone as adjunctive therapy (117). In adults treated with adjunctive dexamethasone, ceftriaxone plus rifampin is the preferred empiric combination regimen because dexamethasone reduces the penetration of vancomycin into the CSF in adults but not in children (118).

In areas with low prevalence of Penicillin Resistant Pneumococci therefore, empiric initial therapy with a third generation cephalosporin is advocated. In areas where pneumococci resistant to extended spectrum cephalosporins are prevalent, empiric therapies with vancomycin and an extended spectrum cephalosporin should be considered, until culture and susceptibility results are known. If the Penicillin MIC for the agent is < 0.1 μg/mL, then therapy can be changed to Penicillin 500,000 units/kg/day alone, which will most often be less expensive and carry less risk of promoting resistance to third generation cephalosporin and vancomycin. Alterna-
tively, the cephalosporin may be continued alone. For intermediate resistant isolate (MIC 0.1-1.0 \( \mu \)g/mL), third generation cephalosporins should be considered alone with vancomycin discontinued. When the MIC equals or exceeds 2.0 \( \mu \)g/mL or when there is little or no clinical improvement, the combination of cephalosporin and vancomycin should be continued. Vancomycin should not be used alone in the treatment of *Streptococcus pneumoniae* associated meningitis (115). Also, chloramphenicol is no longer recommended for use in the treatment of pneumococcal meningitis. Friedland and Klugman (119) demonstrated unfavourable outcome, defined as death, severe neurologic deficit or poor clinical response in 80% (20 of 25) of patients with PRSP meningitis treated with Chloramphenicol, 75-100 mg/kg/day, as initial therapy. Similarly in Dallas, 12 of 16 penicillin resistant isolates of *Streptococcus pneumoniae* from blood or CSF were associated with chloramphenicol minimum bactericidal concentration (MBC) of 8 \( \mu \)g/mL or more, resulting in poor clinical response (120).

In the treatment of otitis media due to PRSP, the elevated MIC for oral \( \beta \)-lactam agents including the new cephalosporins, the relatively low serum concentrations and poor penetration of antimicrobials into the middle ear combined to complicate therapy of otitis media due to these organisms (1, 119, 121). Amoxicillin has been advocated as the drug of choice for the initial treatment of acute otitis media, even in regions with high prevalence of PRSP (109,110,125). Studies have demonstrated relatively high clinical success rate in patients with PRSP associated otitis media ranging from 63% with Amoxicillin in a rural Kentucky study (122) to 82% with Amoxicillin Clavulanate potassium in another large multicentre open labeled trial in the United States of America (123). The clinical efficacy of second-generation cephalosporins, cefuroxime axetil and cefprozil, against pneumococci, have also been demonstrated in some studies (124-126). Barry *et al* (125) recorded 81% (43 of 53) clinical success rate in children with PRSP associated acute otitis media and 92% (152 of 166) in PSSP group.
Gehanno et al (126) also reported success rate of 75% for Penicillin resistant strains, 90% for Penicillin intermediate strain and 93% in Penicillin susceptible strain of pneumococcal acute otitis media in children under five years of age. Based on these studies, it is advocated that Amoxicillin 40 mg/kg/day should be the first line agent in the empiric treatment of acute otitis media in children and adults. In children with recurrent otitis media, who have not responded to Amoxicillin, Amoxicillin-Clavulanate (40 mg/kg/day Amoxicillin and 10 mg/kg/day Clavulanate) or second-generation cephalosporin, such as cefuroxime axetil (30 mg/kg/day) should be considered. For strain refractory to oral agent, injectable second or third generation cephalosporin or vancomycin may be indicated.

In treating Pneumococcal pneumonia due to resistant organism, opinion also differs over the best initial agent. This is as a result of few controlled trials designed to document the outcome in these patients. In a study by Pallares et al (127) and the report of the American Thoracic Society (128), underlying disease appeared to be a more significant risk factor for mortality than the susceptibility to the infecting organism. Hence some authors continue to emphasize the use of injectable Penicillin as a first line agent, claiming that treatment failure is much less likely than in meningitis caused by a strain with the same level of drug resistance (111, 129, 130). Others recommend initial use of cefuroxime, cefotaxime or ceftriaxone (109,111). Based on the available literature (109,111,113,128), it is currently advocated that initial treatment of pneumococcal pneumonia in patients requiring hospitalization should consist of cefuroxime, ceftriaxone or cefotaxime. Therapy can be altered on the basis of the clinical response and not solely on the MIC. If a patient is infected by a non-susceptible strain but is responding to treatment, no change in antimicrobial therapy is necessary. In patients with underlying disease or in community with high prevalence of PRSP, initial therapy should consist of cefotaxime or ceftriaxone and vancomycin. Therapy may be changed depending on the susceptibility of the organism and patient's clinical response.
CLINICAL SIGNIFICANCE OF PRSP INFECTION

The clinical importance of Penicillin resistance among pneumococci appears largely uncertain. Some reports (127, 130) seem to suggest that patient outcomes are similar in individuals with PRSP and PSSP infection, even when the initial therapy consists of a β-lactam antibiotic. Older age and underlying disease appears to be more important factors influencing death from invasive pneumococcal disease than β-lactam susceptibility (127, 128, 131).

However, increase dosages of β-lactam agents is required to produce adequate bactericidal concentration (in view of the elevated MIC) particularly in the CSF and middle ears. Though patient outcome may not differ significantly from sensitive cases, financial costs may be influenced by the large doses required. Patients with hospital-acquired non-susceptible pneumococcal infection were shown by Weis et al (132) to cost an institution approximately $16,000 more to treat than patients with Penicillin susceptible bacteria. (P < 0.05). The difference in treatment costs was attributed to increased patient care requirement such as intensive or critical care beds and nursing services. In a nutshell, infection with resistant organism tend to increase the overall cost of therapy at both individual and institutional level and also increase the risk of toxicity from the increase use of potentially toxic drugs like vancomycin.

PREVENTION OF PNEUMOCOCCAL INFECTION

Patients who are at high risk of acquiring infections by pneumococci such as splenectomized patients, sickle cell anaemia patients, patients with immunoglobulin deficiencies or haematological malignancies should benefit from prophylactic Penicillin V or Erythromycin (98). Bacteraemia with PRSP may however occur in these groups of patient (133).

The use of multivalent polysaccharide vaccines in selected groups such as the elderly has been recommended. The 14-valent pneumococcal vaccines is no longer in use because of its lack of efficacy in children under 2 years of age and only 64% efficacy in children greater than 2 years (134). The currently available 23-valent pneumococcal vaccines contain purified
capsular polysaccharide antigens from 23 serotypes of *Streptococcus pneumoniae*, representing 85-90% of the serotypes responsible for invasive disease in children and adults in the United States (135,136). Of the seven serotypes most commonly associated with drug resistance, six are represented in the vaccine. Some degree of protection is provided against serotype 6A that is absent in the vaccine because of serologic cross-reactivity with serotype 6B that is present in the vaccine (137). Because of the emergence of drug-resistant pneumococcal infection, there is need for adherence to the recommendation of the Advisory Committee on Immunization Practices (ACIP) that persons 2 years and above, with medical conditions placing them at increased risk for pneumococcal infection and all persons 65 years and above, should receive the 23-valent pneumococcal vaccines (138,139).

Children under the age of 2 years are especially susceptible to invasive pneumococcal infections and are at an increased risk for drug resistant infection. Commercially available polysaccharide vaccines are not able to elicit adequate immune response in young children under 2 years of age. This has led to the development of pneumococcal capsular polysaccharide-protein conjugate vaccine that employ the same principle used in *Haemophilus influenzae* type b vaccine; coupling the polysaccharide to a carrier protein, which increases immunogenicity (140,141).

Preliminary antibody titre result shows these vaccines, containing many serotypes, to be safe, and consistently elicit an immunologic response in infants as young as two months (140,141). In February 2000 (142), a conjugate vaccine for seven pneumococcal serotypes was licensed for use in infants and children, and is now recommended in the United States for all children less than 2 years of age, with catch-up vaccination schedules suggested for children 2 to 4 years of age (143).

**OTHER CONTROL MEASURES**

Surveillance for drug resistant *Streptococcus pneumoniae* should be initiated in all institutions and communities. In some states in the United States of America (56), state-wide surveillance for drug resistant *Streptococc-*
*C. pneumoniae*, as a notifiable condition, has been initiated. The Centre for Disease Control and Prevention (CDC), in collaboration with the Council of State Territorial Epidemiologists and Public Health Laboratory Directors, is helping to develop strategies for collecting information on PRSP in other states and for preventing morbidity and death associated with infection with these strains. Eradication of carrier states may also be an option to reduce level of resistance in community (60). Attempt at eradication with rifampicin and erythromycin carried out mainly in South Africa was successful in 96% of carriers while only 74% success rate was recorded with vancomycin (144). In areas with high prevalence of PRSP, there is at present, no rationale for treatment of carriers, as its value in outbreak situations remains largely unproven (15).

**PROBLEMS OF PRSP IN AFRICA**

Little is known about the prevalence of PRSP in Nigeria and many other African countries apart from South Africa. Most health institutions in Africa lack active antimicrobial resistance surveillance, drug monitoring and infection control programmes. There is therefore apparent lack of awareness by health care providers, of the occurrence of PRSP and other resistant organisms, and their clinical significance. Added to this is the poor laboratory service in many centres, to identify and perform susceptibility testing (145).

With poor socioeconomic situations in many African countries, occasioned by bad governance, there is gross under funding of the health sector. Little attention is paid to infectious disease surveillance and control programmes, an aspect of medicine that has not been well appreciated by many authorities. Superimposed on this, is the lack of regulation on antibiotic prescription and usage. Self-medication and over-the-counter prescription of antibiotics is widespread in Nigeria and many African countries (145,146). The problem of drug resistance is therefore expected to be enormous in these countries. A limited survey in 1978 gave a PRSP prevalence rate of 20% in Nigeria (65). This has a grave implication for therapy of serious pneumococcal infection in this country. Based on this and the
available literatures from other Africa countries (10,13,61,71,98) and elsewhere (109-114), penicillin will no longer be recommended in the initial (empiric) therapy of serious pneumococcal infections in Nigeria. Ceftriaxone and cefotaxime are the preferred agents in the initial empiric therapy of pneumococcal infections of the lungs, blood stream and the central nervous system.

There is the need to increase surveillance for PRSP in health institutions and communities to determine the true prevalence and evaluate their susceptibility to newer agents. Antibiotic prescription practice should be regulated by law, with outright ban on over-the-counter sale of antibiotics. Laboratories should make available, reports of susceptibility pattern of common pathogens in the environment to the physicians and other health care providers on a regular basis. There should be a coordinated action between the various health institutions and the National Infection Control Centre, which should be responsible for storing data on susceptibility and occurrence of PRSP and other resistant organisms.

**CONCLUSION**

Since there is no doubt that imprudent use of antimicrobials promotes the spread of drug resistance in both the hospital and the community, the emergence of drug resistant *Streptococcus pneumoniae* is hardly surprising. Although appropriate antimicrobial use has unquestionable value, providing antimicrobials for viral infections of the upper respiratory tract does not benefit patients, it rather increases the likelihood that resistant organisms will be selected. Many instances of “presumed bacterial infection” are likely to be of viral aetiology but are misdiagnosed because of inadequate diagnostic criteria used by the physician. Physician concern over inadequate treatment for presumed bacterial infection, combined with patient pressure for prescribing antimicrobials, further complicates the problem as does the use of more expensive, broad spectrum agents, which may not be necessary unless indicated by organisms’ identification and susceptibility.

The primary responsibility for identification, management and control of the spread of drug resistance pneumococcal infection lie.
with the primary care physician and diagnostic laboratory. Laboratories must be equipped to isolate and perform susceptibility tests and must participate in external quality control programmes. The presence of Penicillin intermediate and resistant Streptococcus pneumoniae, as well as the status of other drug classes must be known in each community and updated frequently to help guide empiric therapy of infections potentially caused by these organisms since organism detection and in vitro testing may not be available most of the time.

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