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Penicillin – Resistant Pneumococcus

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SUMMARY

Penicillin-resistant *Streptococcus pneumoniae (pneumococcus)* became clinically significant in the late 1970's when reports of resistant clinical isolates, leading to treatment failure, were first reported from South Africa. Since then reports of penicillin–resistant pneumococcus (PRP) have come in from all over the world including Africa. The drugs of choice for treatment of life-threatening infections like meningitis and septicaemia were changed to cefotaxime and ceftriaxone. In recent times, there has emerged pneumococcal strains resistant to most antibiotics including the extended spectrum cephalosporins with grave implications for therapy. The penicillin resistance is not due to the production of beta-lactamases but to changes in the penicillin binding proteins, brought about by genetic transformation. This is a review of the literature on the epidemiology, diagnosis, therapy and prevention of PRP including the problems encountered in Nigeria in isolating and identifying these strains.

Key Words: Pneumococcus, Penicillin-Resistant.

Historical and Epidemiological Review

In 1875, Klebs described *Streptococcus pneumoniae (pneumococcus)* in the fluid from the lungs of a man dying with pneumonia[1]. In 1881, Pasteur and Stenberg independently recovered pneumococci from rabbit that had been experimentally inoculated with saliva[2]. Over the next 10 years it was shown to cause infection of the cerebrospinal fluid (CSF), kidney, middle ear, blood, synovial fluid, heart valves and pericardium [1, 2]. The association of the pneumococcus with lobar pneumonia was described by Friedlander and Talman in 1883 and was later confirmed by Frankel in 1884 and Weichselbaum in 1886[3]. By 1910, Neufeld and Handel reported that antisera conferred type-specific immunity in mice[3]. In 1962 it was recognized that a large proportion of healthy persons carried the pneumococci in the nasopharynx and that this was often a source of disease in contacts of these asymptomatic carriers[5, 6].By 1939, *S. pneumoniae* was described as the aetiological agent in 90% of all cases of lobar pneumonia. Between 1944 – 1945 the first successful field trial of a polyvalent (tetravalent) polysaccharide vaccine for pneumococcal pneumonia was carried out by Macleod and co-workers in a military training centre in which an outbreak of pneumococcal pneumonia had been detected[4].

In the pre-antibiotic era, the mortality of bacterial pneumococcal pneumonia was 77%[8]. With the introduction of sulphonamides in the 1930's and penicillin in 1945, antimicrobial therapy replaced the immune sera for the treatment of pneumococcal infection and mortality decreased dramatically[9]. Between the 1950's and 1970's, the mortality rate was stable at about 28%[10, 11]. In the 1960's, the susceptibility of the pneumococcus to penicillin and tetracycline was considered invariable[10], but by the 1970's the occasional resistant strain was encountered[12] but was not considered significant or a sign of an emerging trend[13].

Antimicrobial resistance in the pneumococcus was first documented by Morgenroth and Kaufman in 1912[14], when optochin–resistant pneumococci were obtained from experimentally infected mice treated with optochin (ethylhydrocupreine). Acquired pneumococcal resistance to optochin during therapy of patients was reported in 1915[15]. In 1939, *S. pneumoniae* resistance to sulfapyridine was reported in a patient with meningitis[16] who died despite high concentrations of the drug in her cerebrospinal fluid (CSF). In 1943 sulfadiazine resistance was reported in a patient during drug therapy for lobar pneumonia[17].

Although mutant strains of S. pneumoniae resistant to penicillin G were reported soon after the introduction of this drug in 1945[18], clinical resistance was not reported till 1965 in a Boston hospital in the USA, in two of 200 strains, but they failed to recognise its significance[19]. Hansman and Bullen in 1967 noted the significance of penicillin-resistance in the pneumococcus[21]. This strain, with an MIC of 0.06µg/ml was isolated from the sputum of a patient who presented with hypogammaglobulinaemia and who had been exposed to multiple antibiotics[20, 21].

Subsequently, resistant strains were reported from New Guinea and Australia [22, 24] and gradually anecdotal descriptions of pneumococci with increased resistance (most were of intermediate resistance) began to appear in literature. All the patients were children below the age of 5 years and most had a concomitant debilitating disease [25–29].

In 1977 – 1978, penicillin - resistant pneumococci (PRP) were detected in Durban, South Africa, among patients with meningitis, bacteremia, pneumonia and empyema[30, 31]. All isolates were highly resistant to penicillin with MIC's of 4 – 8 µg/ml and were also resistant to 3 or more classes of antibiotics. The widest spectrum of resistance in a single organism was resistance to 7 classes of antibiotics i. e. resistance to beta-lactams (including penicillin and first and second generations of cephalosporins), tetracyclines, macrolides, (erythromycin), clindamycin, chloramphenicol, rifampicin and cotrimoxazole, These strains were isolated from hospitalised children and at that time more than 50% of 128 hospitalized carriers of pneumococci were colonised with strains resistant to penicillin, tetracycline, erythromycin, chloramphenicol and co-trimoxazole[31].

Between 1974 and 1984 penicillin–resistant *S. pneumoniae* were reported worldwide from Israel, Spain, Poland, South Africa and the USA[32]. Through the 80's and into the 90's reports increased from many countries including New Zealand, Switzerland, West Germany, France,

Belgium, Hungary, Romania, England, Iceland, Japan, Malaysia, Pakistan, Bangladesh, Chile, Brazil and Canada[30].

Reports from Africa are scarce except from South Africa in which resistance rates are close to 20%[30]. Surprisingly, only low rates <5% have been obtained in surveys carried out in Zambia,[33] Senegal and Ivory Coast[34]. These may be as a result of underreporting and more surveys will be required in these countries. In Nairobi (Kenya), a rate of 26% has been reported[35]. North African countries have also posted low rates, below 2% in Morocco and Egypt though in Tunisia resistance is approximately 10%[34]. A limited survey in 1978 from Nigeria reported a 20% revalence rate of PRP[36].

Recent studies suggest that with time resistant strains increase their geographic spread and level of resistance[37,38,39], and by 1991, Bradley reported the first case of a strain resistant to a third generation cephalosporin, ceftriaxone[40] which was confirmed by reports came in from South Africa in 1993.[41]

Serotypes

There are al least 84 different serotypes of *S. pneumoniae* based on differences in their polysaccharide capsules[9]. Pneumococci may be serotyped by the Quellung reaction of the capsular polysaccharide[3]. According to the Danish nomenclature, the serotyping scheme is based on reaction to 48 antisera. Some antisera recognise a specific serotype (e. g., serotype I) while others recognise multiple serotypes within a serogroup (e.g. 6A and 6 B).[3]

The distribution of Serotypes associated with disease varies geographically and with age in that children have different distribution of disease-causing serotypes than adults.[42,43] Of the 84 capsular types, types 1, 3, 4, 7, 8, 9, 12, and 4 usually cause the most serious diseases in adults while serotypes 4, 6, 18, 19, 23, 1, 4 and 9 are more commonly associated with serious infection in children[3].

Definition of Resistance and Susceptibility

Until the emergence of penicillin resistant *S. pneumoniae*, susceptibility testing of the pneumococci was regarded as unnecessary. Since the emergence of high level penicillin resistance strains, susceptibility testing is now essential. The recommendation of the National Committee for Clinical Laboratory Standards (NCCLS) has become the standard criteria for the determination of susceptibility to any antibiotic (Table I). These breakpoints (point at which strains are considered resistant) are applicable only if these tests. are carried out in broth dilution using the appropriate media (cation-adjusted Mueller – Hinton broth with 2-5% lysed horse blood).

Pneumococci have penicillin MIC's at all concentrations from 0.008–8μg/ml and do not have any clearly defined populations at any specific MIC[57]. Susceptibility of S. pneumoniae to penicillin G is defined as an MIC ≤ 0.06 μg/ml, intermediate (relative resistance) as an MIC of 0.1-1.0 μg/ml and high level resistance as an MIC ≥ 1.0 μg/ml[58].

MIC breakpoints recommended for pneumococci by the NCCLS[59] are applicable to erythromycin, tetracycline and cotrimoxazole (see table I) as strains are generally either susceptible or resistant. Strains with intermediate MIC's are rare and should be considered resistant.[56,59,60,61,62] The breakpoint for chloramphenicol is 4μg/ml and correlates well with the absence or presence of chloramphenicol acetyltransferase[63].

Breakpoints for oral cephalosporins were also proposed by the NCCLS in December 1993[56] but were found to be too high and were not substantiated by clinical studies on penicillin-intermediate or resistant strains. These breakpoints were removed from the 1994 supplement[59] except for that of cefuroxime axetil for which clinical data was available[64]. Penicillin susceptible strains are susceptible to oral cephalosporins and these agents therefore do not need to be tested against these strains. Of currently available betalactams, cefotaxime, ceftriaxone and imipenem are the most active in-vitro against PRP[65,66,67]. The MIC range for third generation parenteral cephalosporins is < 0.5μg/ml for susceptible strains. 1μg/ml for intermediate and ≥2μg/ml for resistant strains[50].

Highlevel Penicillin Resistance and Multiple Drug Resistance

Pneumococcal resistance may occur alone or in combination with resistance to other antimicrobial agents. Resistance to antibiotics of at least three different groups has been defined as multiple resistance.[31,32] High level penicillin resistance i. e., MIC ≥ 2.0 μg/ml and multiple resistant strains are recognised only among a few pneumococcal serogroups. High level resistance and multiple resistance have been associated mainly with serotypes 6A, 6B, 19A,[44,45,46,47] 19F, 14[48,49] and 23[50,51,52]. Other serotypes that have been identified include serotypes 1. 3, 5, 15, 31 and 35[32].

Intermediate Resistance to Penicillin.

The same serogroups which dominate high level, multiply-penicillin resistance are also the commonest serogroups associated with intermediate resistance i. e., MIC ≥ 0.1 μg/ml. But the spectrum has expanded such that virtually all commonly isolated serogroups have now been found to manifest intermediate resistance[32]. These serogroups include 1, 2, 3, 4, 6(A+B), 7(F), 8,9(N), 10F, 11(F and A), 13, 14, 15, (F, B, C), 16, 17(F), 18 (F, C), 19(F, A), 21, 22(F), 23(F, A), 24(F), 33, 34 and 35(F)[32].

It is necessary to emphasize that despite the diversity of reported serogroups, only a few serogroups dominate the whole spectrum and these differ between geographic locations, e. g., in the USA the most common serotypes affected in this spectrum appear to be 19A and 14[32] while in South Africa most resistant strains belong to serogroups 6, 19, or 14[53].

Resistance to other Antimicrobial Agents.

Resistance to erythromycin and chloramphenicol appear to be restricted to the same serogroups involved with multiple resistance to high level penicillin resistance[32]. There is limited information on the spectrum of Co–trimoxazole and rifampicin but it will appear that resistance is spread widely amongst serogroups[53, 54]. Tetracycline resistance has been recognised in more than 20 serogroups[55].

Risk Factors for Carriage of Penicillin Resistant Pneumococci

Risk factors for carriage and infection by PRP include age (mostly in children less than 5 years)[32], hospitalisation[32,58], prior exposure to antibiotics[32,66, 49] and patients with immunodeficiency and other underlying diseases especially measles, malnutrition, gastroenteritis and tuberculosis[30]. There is no doubt that the acquisition of pneumococcal disease is increased in the presence of immune deliciency or underlying disease states. Diabetes mellitus, chronic infections of the cardiovascular system or respiratory tract, chronic renal failure, Nephrotic syndrome, organ transplants, some malignancies (Hodgkin's lymphomas, multiple myeloma), HIV infection and certain neurological conditions have all been associated with an increased risk of pneumococcal infection[97]. The association between underlying disease and penicillin-resistant pneumococcal infection is not proven because most of these children are also hospitalized for prolonged periods and the contribution of prolonged hospitalization to the acquisition of PRP in patients with chronic disease cannot be ruled out[32].

Mechanisms of Penicillin Resistant

As with many bacterial strains, the rapid appearance of multiple antibiotic resistance in pneumococci is due to the ability of resistance genes to be horizontally transferred. To date, beta–lactamase producing pneumococci have not been reported. Resistance to beta–lactams is entirely due to the development of high molecular weight penicillin binding proteins (high Mr PBP's) that have reduced affinity for beta–lactam antibiotics[9,10]. This resistance appears to have been brought about by genetic transformation and is chromosomally mediated.

This penicillin resistance is mediated by changes in the affinity or rate of acylation of enzymes known as PBP's. These enzymes (proteins) are believed to catalyze the terminal stages of murein synthesis[67] and are inhibited by covalent bonding with penicillin at their site. Six PBP's are found in susceptible strains with only rare exceptions to this pattern (PBP 1a, 1b, 2x, 2a, 2b and 3)[68, 69]. All are high Mr-PBP except 3 and this is not thought to be involved with the killing action of beta-lactam antibiotics[70]. In fact PBP 2b inhibition results in cell lysis which is thought to be the lethal target in pneumococci[57]. Highly resistant penicillin-resistant strains appear to possess low affinity forms of PBP 1a, 2a, 2x, 2b and perhaps 1b[71,72].

Multiple resistance to other agents can be transferred by conjugation in the pneumococci[32]. A transposon TN 1545 has been identified in resistant strains and confers resistance to chloramphenicol, erythromycin, tetracycline and kanamycin[63]. Tetracycline resistance is due to production of a protein that binds to the ribosome and blocks protein synthesis while chloramphenicol resistance is due to the production of an inducible chloramphenicol acetyltransferase[63]. Altered ribosomal affinity has also been found to be responsible for streptomycin and erythromycin resistance in many penicillin resistant strains[63]. Resistance to trimethoprim on the other hand is believed to be mediated by an altered dihyrofolate reductase enzyme with decreased affinity for trimethoprim[73, 32] but the details of this resistance in the pneumococcus has not yet been elucidated. To date, no specific details on rifampin resistance have been reported though it is believed to be based on an altered DNA–dependent RNA polymerase[73, 32].

Laboratory Diagnosis of Antibiotic Pneumococci

Most pneumococci are readily identified but some strains with atypical features such as: formation of rounded colonies (rather than flat or concentrically ringed), optochin resistance or the absence of capsules may be misidentified as viridans streptococci[74]. These atypical strains are more likely to be encountered from sites with normal flora or among penicillin-resistant strains[60]. Strains with zones of inhibition of ≥13mm can be presumptively identified as pneumococci[32,74]. Incubation in air with added CO_2 causes a decrease in zone size around optochin disks which is reversed when pneumococci but not viridans streptococci are incubated in air[75].

Choice of Agents for Susceptibility Testing

This usually depends on the nature and severity of the pneumococcal infection, the clinical practices of the physicians, the requirement for oral parental agents, cost and availability of antimicrobials, use of empiric regimens and knowledge of susceptibility to related agents[60]. Agents suggested for initial testing include penicillin G, chloramphenicol, erythromycin, tetracycline and co-trimoxazole. In addition, if there is penicillin resistance a third generation cephalosporin (such as cefotaxime, ceftriaxone) or imipenem and vancomycin may also be tested. Oral cephalosporins except cefuroxime axetil should not be tested till clinically relevant breakpoints for these agents are developed[57].

Susceptibility Testing Methods.

A disk diffusion test with a penicillin disk is likely to give misleading result as it may show a wide zone of inhibition even in resistant strains. Initial screening for PRP is best performed by disk diffusion using a 1µg oxacillin disc or 5µg methicillin disc with cut-off zones of 20mm or 25mm respectively[60]. The MIC's of strains with zones smaller than these should be tested for penicillin or if clinically indicated, cetotaxime and ceftriaxone using a standard method[60] and for selected agents by disc diffusion[60,76,77]. This will determine the degree of penicillin resistance and the presence or absence of high-level resistance[57].

Determination of the Minimum Inhibitory Concentration

The agar dilution method is regarded as the reference method for determining the Minimum Inhibitory Concentration (MIC) for pneumococci[60]. This is carried out in Mueller - Hinton agar supplemented with 50% whole defibrinated sheep or horse blood or 5% lysed and centrifuged horse blood for sulphonamides [57, 60, 78]. The inoculum size is 10^4 colony forming units (cfu) per spot and plates are incubated in air or added CO_2 (5 –10%) overnight[77] though other methods have been described[56].

In recent times, a new method for MIC testing was

introduced into the market - the E-test (AB Biodisk, Solna, Sweden). This method consists of a calibrated antibiotic-impregnated plastic strip which is applied to the surface of an inoculum-coated agar plate. An antibiotic gradient is produced which results in an ellipse of inhibition. The point at which the ellipse meets the strip is the MIC. Evaluation of the E-test has shown excellent correlation with agar dilution and microdilution methods for penicillin G, cefotaxime, ceftriaxone, amoxilillin, chloramphenicol, erythromycin and tetracycline, though the MIC for penicillin G tends to be slightly lower resulting in some resistant strains being catergorised as intermediate [57, 61, 79, 80].

Disc diffusion has been well standardised for the testing of pneumococci against selected agents[58, 77, 81,100] and the distinction between susceptible and resistant strains has been well delineated by the NCCL's 5th information supplement published in December 1994[59] (Table 2). It should be noted that strains with MIC's of 0.06µg/ml usually have oxacillin zones of 7-19mm and therefore cluster with resistant strains[60]. For co-trimoxazole, susceptibility breakpoints of < 0.5 / 9.5µg/ml for MIC and > 15mm for disc diffusion and agar dilution methods worked well on Mueller–Hinton agar with 5% whole sheep blood or 5% lysed horse blood[82].

Interpretation and Implications of MIC results for Therapy

The MIC's of Penicillin G and other beta–lactams are generally directly related and the MIC's of these agents increase in parallel with those of penicillin G[57, 83]. However susceptible strains may not respond clinically in meningitis or to oral therapy of otitis media due to poor drug penetration into the meninges and middle ear or because of low drug levels following oral administration[57]. Based on current knowledge, penicillin resistant and intermediate resistant strains should be considered resistant to Penicillin G in meningitis and to all oral beta-lactams for the treatment of all infections.

Pneumococci are regarded as susceptible to parenteral third generation cephalosporins (cefotaxime and ceftriaxone) if MIC's are ≤ 0.5µg/ml, of intermediate resistance if MIC's are 1µg/ml and resistant if 2µg/ml. Non-meningeal, systemic infections should therefore be responsive to therapy with these parental third generation cephalosporins if MIC's are ≤1µg/ml. In meningitis, cefotaxime and ceftriaxone continue to be the drugs of choice if MIC≤ 0.5 µg/ml, but meningitis caused by strains with intermediate MIC's may respond inadequately and such cases should be treated with maximum dosage of these agents and the addition of vancomycin or rifampin should be considered. Where high-level third generation cephalosporin resistance is prevalent, maximum dosage of cefotaxime or ceftriaxone plus vancomycin or rifampin is suggested for empiric therapy of meningitis[57].

The interpretation of the MIC's of vancomycin is unclear due to problems associated with penetration of vancomycin into the central nervous system (CNS) and lack of clinical data on systemic infection. However, the MIC of this agent is in a very narrow range (0.25-1µg/ml) and strains with MIC's in this range can be considered susceptible in systemic infection[57]. The same holds for imipenem with breakpoints of ≤ 0.12 for susceptibility and ≥ 1µg/ml for resistance[57]

Treatment

Treatment of resistant pneumococcal infection is complicated by factors such as delay in recognising the presence and degree of resistance in strains, variability of drug levels at different sites particularly in the CSF, natural history of the disease at different sites and in different age groups, stage of infection at which initial or appropriate therapy is initialised and the presence of underlying conditions such as malnutrition, immunodeficiency or malignancy[32,57,60]. Little prospective data is currently available to guide clinical use, and most recommendations are still tentative and largely empiric[57]. Meningitis and overwhelming bacteraemia are the most serious forms of this disease and least responsive to therapy due to poor penetration of the CSF or massive bacterial load in bacteraemia[57].

Clinically, patients with meningitis due to PRP (MIC > 1µg/ml have shown clinical failure of penicillin G therapy [84,85], but some with intermediately resistant strains have responded to high dose penicillin therapy (500,000 units/kg/day)[64,65]. Chloramphenicol 100mg/kg/day has recently been reported to show clinical failure in cases caused by penicillin–resistant but chloramphenicol-susceptible strains[67] it has been postulated that these failures may be due to the loss of autolysis seen in PRP causing chloramphenicol to be bacteriostatic rather than bactericidal[63,67,68]. In some cases in adults, vancomycin (30-45mg/kg/day) has yielded disappointing results which has been associated in some cases to variable levels of the drug in the CSF[65]. Cefotaxime at 250-350 mg/kg/day in adults has shown fairly good results in patients with meningitis caused by strains that are highly penicillin-resistant even with MIC's as high as 4µg/ml (7 cures, 1 relapse and 1 death)[65].

Assessment of the results of therapy for meningitis caused by resistant pneumococcal strains in adults is complicated by the variety of this disease in this population and the high mortality even with susceptible pneumococcal strains[5,57]. In 1987, a consensus report on therapy of pneumococcal meningitis in infants and children recommended cefotaxime, ceftriaxone or vancomycin for strains relatively resistant to penicillin but did not address the issue of highly resistant strains[69]. The use of imipenem 400mg/kg/day has been reported in one paediatric case of meningitis caused by an intermediate resistant strain, where the agent was successful in treating the second relapse of the infection[70] but this agent has been reported to cause seizures in some patients[71], although it is not clear that the incidence of seizures is higher than with other beta-lactams[72]. Metropenem, a similar drug, has been shown to be effective in the treatment of meningitis caused by resistant strains without causing CNS side-effects[73].

In bacteraemia caused by intermediate-resistant pneumococci, treatment with high doses of intravenous penicillin G (150,000-250,000 units/kg/day) is recommended in adults[75]. Optimal therapy both for acute otitis media and prevention of recurrent otitis media remain controversial [78,79] but is has been shown in one study that recurrent otitis mediawas associated with penicillin resistant strains

and also associated with prophylactic antibiotic usage[76]. Recently, amoxicillin has been suggested as a potentially useful drug for penicillin intermediate and even resistant strains[86] and clinical evaluation is still in progress. The use of cefuroxime-axetil has been studied in PRP but is still uncertain[14]. No specific recommendations have been made for the treatment of otitis media due to PRP and treatment of individual cases are best based on in-vitro susceptibilities of the infecting strain[57].

Prevention of Pneumococcal Infection

High risk patients i. e., patients at risk of overwhelming pneumococcal sepsis e. g., splenectomised patients, those with sickle cell anaemia, immunoglobulin deficiencies or haematological malignancies, benefit from prophylaxis with penicillin V or erythromycin[60], though breakthrough bacteraemia with a penicillin-resistant strain of *S. pneumoniae* has been reported[91].

Use of multivalent polysaccharide vaccines in selected groups such as the elderly has also been recommended[92-94]. Use of the 14-valent pneumococcal vaccine is limited because of itslack of efficacy in children less than 2 years and efficacy is only 64% of those > 2 years[92]. The currently used 23-valent pneumococcal vaccine has a wider efficacy of >85%[94] but also does not protect children <2yrs. The immunogenicity of protein-coupled pneumococcal capsular vaccines have been studied[95] and have shown potential for their use in children <2yrs old so further work is in progress[60].

Treatment of Carrier States and Other Control Measures

Surveillance for resistant pneumococci should be instituted in all centres with increased attention paid to limiting unnecessary use of antibiotics. In hospital outbreaks, affected patients may have to be isolated to limit spread in communities where resistant strains are not widespread in the hospital or community. Eradication of the carrier state may also be an option to reduce the levels in the community. Most of tho work on eradication of the carrier state was carried out in South Africa [58,96] and was based on the susceptibility of their local strains[96]. Success of therapy was assessed as three consecutive nasopharyngeal swabs negative for PRP in the week following therapy[96]. Erythromycin and Rifampin (45mg/kg/day and 20mg/kg/day) was 96% successful while Vancomycin 45mg/kg/day for 5 days was 74% successful[96]. In endemic areas there is at present no rationale for treatment of carriers and its value in outbreak situations remains unproven[32].

CONCLUSION

With the poor economy in this country, the isolation and identification of PRP remains a problem. In the past few years only a few strains of S. pneumoniae have been isolated in the Lagos University Teaching Hospital and they were not tested for penicillin resistance. Only one report exists in the literature from Nigeria on PRP. In this study in 1978, which was quite limited, a 20% prevalence rate was recorded[36]. This has great implications for therapy and suggests that tor Nigeria, penicillin should no longer be used as empiric treatment for serious pneumococcal infections.

Lack of awareness among clinicians and laboratory workers about the occurrence of PRP and the habit of starting therapy before sending samples to the microbiology laboratory, have contributed to the lack of data on this subject. This has been compounded by the economic downturn leading to low patient turnout, inadequate funding of hospital laboratories and low morale of laboratory workers.

Abuse and misuse of antibiotics are risk factors for the carriage of PRP and this is a common problem in the country[104,105]. This, with the increasing incidence of HIV in the country and the attendant pool of immunosuppressed patients in whom the risk of acquiring life-threatening PRP infection has been shown to be 100% - 300% higher than the normal population[98,99], increase the probability for the presence of PRP in Nigeria. Considering all these facts it is the opinion of this author that in this environment life-threatening infections due to the pneumococci (meningitis and bacteraemia), should be treated empirically with cefotaxime or ceftriaxone pending the results of properly performed susceptibility tests. This recommendation is based on data obtained from the trends observed in other African countries (which show rates of up to 30%) and elsewhere[35,101,102].

There is a need to improve the isolation and identification of penicillin-resistant *Streptococcus pneumoniae* in our environment by using antibiotics more judiciously not only in public hospitals (at all levels) but more importantly in private health institutions where a large percentage of the population are treated. This will require viable antibiotic guidelines which take into consideration the antibiotic susceptibility patterns of local bacterial strains. These guidelines will be reviewed regularly based on the changing antibiotic susceptibility patterns. Their use will reduce, if properly implemented, the cost of antibiotic treatment by reducing the incidence of "failed therapy" and also reduces on the long run the incidence of antibiotic resistant organisms.

Table I

NCCLS recommended MIC breakpoints for susceptibility testing of *Streptococcus pneumoniae*

Agent	Breakpoints		
	Susceptible	Intermediate	Resistant
Penicillin G	≤0.06	0.1-1	≥2
Cefotaxime	≤0.5	1	≥2
Ceftriaxone	≤0.5	1	≥2
Cefuroxime Axetil	≤0.5	1	≥2
Imipenem	≤0.12	025-0.5	≥1
Azithromycin	≤0.5	1	≥2
Clarithromycin	≤0.5	1	≥2
Clindamycin	≤0.25	0.5	–
Erythromycin	≤0.5	1-2	≥2
Chloramphenicol	≤4	–	≥8
Ofloxacin	≤2	4	≥8
Tetracycline	≤2	4	≥8
Cotrimoxazole	≤0.5	1	≥4
Rifampicin	≤1	2	≥4
Vancomycin	≤1	–	–

(From NCCLCS 5th informational supplement, table 2c of standard M7-A3).

* These standards are only relevant if tests are carried out on cation-adjusted Mueller–Hinton broth with 2 - 5% blood.

Table II

NCCLS recommended disk difusion zone diameter breakpoints for susceptibility testing of *Streptococcus pneumoniae*

Agent	Disk content (µg)	Zone diameters (mm)			Breakpoints (µg/ml	
		Resistant	Intermediate	Susceptible	Susceptible	Resistant
Penicillin	1 (oxacillin)	–	–	≥ 20	<0.06	≥ 2
Azithromycin	15	≤13	≤14 – 17	≥ 18	≤ 0.5	≥ 2
Clarithromycin[1]	15	≤16	≤17 – 20	≥ 21	≤ 0.05	≥ 2
Clindamycin[1]	2	≤15	≤16 – 18	≥ 19	≤ 0.25	≥ 1
Erythromycin[1]	15	≤15	≤16–20	≥ 21	≤ 0.5	≥ 4
Chloramphenicol[4]	30	≤20	–	≥21	≤ 4	≥8
Ofloxacin	5	≤12	≤13 – 15	≥16	≤ 2	≥8
Tetracycline[2]	30	≤17	≤18 – 21	≥ 22	≤2	≥ 8
Cotrimoxazole[2]	1.25/23.75	≤15	≤16 – 18	≥ 19	≤ 0.5	≥4
Rifampin	5	≤16	≤17–18	≥ 19	≤ [1]	≥4
Vancomycin[3]	30	–	–	≥ 17	≤ 1	–

(From NCCLS 5th Informational supplement table 2 c of standard M2-A5.

* Oxacillin represents all beta-lactams.

[1] All strains with high level erythromycin resistance are resistant to all macrolides, lincosamides and azalides, Intermediate strains are rare.

[2] Intermediate strains are rare, best considered resistant with oral therapy.

[3] All strains that yield results not within thesusceptible category should be submitted to a reference laboratory for further testing.

[4] All penicillin resistant strains should not be used for treating meningitis even if the strains appaer chloramphenicol-susceptible.

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