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Bacteriological evidence of antibiotic failure in pneumococcal lower respiratory tract infections

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ABSTRACT: The global pandemic of antimicrobial resistance, particularly in the pneumococcus, has had a major impact on the management of community-acquired pneumonia.

A number of prospective and retrospective studies have analysed the impact of penicillin resistance on clinical outcome in pneumonia. Pharmacodynamic principles predicting success when the antibiotic dose exceeds the minimum inhibitory concentration (MIC) for 40–50% of the dosing interval have proved remarkably accurate. There is no evidence of bacteriological failure of penicillins active against resistant strains. There is a single report of the failure of the less active agent, ticarcillin. High dose oral and intravenous amoxicillin should treat strains with MICs $\leq$4 μg·mL^{-1}, as should high doses of intravenous penicillin, ceftriaxone and cefotaxime. Strains of pneumococci resistant to these agents at an MIC $\geq$8 μg·mL^{-1} are rare at the present time. Most other cephalosporins are less active and should not be used empirically for drug-resistant *Streptococcus pneumoniae*. Bacteriological failures of cefazolin, cefuroxime and ceftazidime have been reported.

There is increasing evidence of bacteriologically confirmed macrolide failure of pneumonia therapy at MICs $\geq$4 μg·mL^{-1}. The molecular basis of the resistance is irrelevant if the MIC is in that range or higher. Double mutants in the *parC* and *gyrA* genes lead to fluoroquinolone resistance that has been found to cause bacteriological failure of the fluoroquinolones, particularly levofloxacin and ciprofloxacin, in the management of pneumonia and exacerbations of chronic bronchitis. Two mutations in these genes can greatly increase the MICs of all the marketed fluoroquinolones, and raise the prospect of failure of therapy even with the more active ones. However, demonstration of bacteriological failure of gatifloxacin or moxifloxicin has not yet been reported.

High dose, active β-lactams or fluoroquinolones with enhanced activity against Gram positive pathogens remain the drugs of choice for the management of community-acquired pneumonia caused by the drug-resistant pneumococcus.

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Low levels of penicillin resistance in the pneumococcus were first described in Australia during the 1960s [1], and multiple and high-level resistance (defined as a penicillin minimum inhibitory concentration (MIC) $\geq$2 μg·mL^{-1}) were first described in South Africa in the 1970s [2, 3]. At that time, it was widely assumed that there was a direct relationship between *in vitro* resistance and clinical failure. Indeed, a number of reports, for example that by FELDMAN *et al.* [4], documented the failure of therapy associated with mortality in adults with pneumonia, infected with penicillin-resistant strains. However, it has been apparent for the past 40 yrs that there is 5% mortality in bacteremic pneumococcal pneumonia that has not been altered by appropriate antimicrobial therapy [5]. These data date back from the days when there were no resistant pneumococci described. Therefore, the concordance, of clinical failure and antibiotic resistance will occur by chance in 5% of patients infected with antibiotic-resistant pneumococci. Any analysis of the impact of resistance on outcome needs to be stratified for confounding variables, such as an association between resistance and severity of disease. As resistant strains are commonly associated with hospitals and nosocomial infections [6], there is a greater chance of immunocompromised patients being infected with resistant strains [7, 8]. The most important predictor of outcome in pneumonia is severity of disease, and it is therefore critical to the analysis of outcome to stratify cases for severity of disease [9]. It is also essential that careful information is obtained about the exact dose and duration of antimicrobial received before failure is documented. The best indicator of the failure of an antibiotic is the persistent presence of bacteria. This is difficult to document in the majority of patients with pneumonia. Persistent presence of bacteria in purulent sputum is highly suggestive of bacteriological failure, but may be confounded by the contamination of sputum with saliva and the detection of colonising rather than pathogenic strains. Persistent bacteremia

is unequivocal proof of bacteriological failure, but repeated blood cultures are seldom taken once therapy has been commenced. The bacteriological documentation of failure has therefore rarely been proven. This review will describe the principles of the pharmacodynamics of treatment of pneumococcal pneumonia and will discuss the various studies performed to date, describing the failure, or lack there of, of various classes of antimicrobials for the management of pneumococcal pneumonia.

β-lactam agents

An analysis of early reports of penicillin failure in the management of pneumococcal pneumonia revealed no bacteriological evidence of the failure of penicillin in this therapeutic setting [10]. A large prospective series of patients from Spain showed no difference in the 30-day mortality of patients treated with β-lactam agents, when patients infected with strains resistant to penicillin were compared with patients infected with susceptible bacteria [11]. Although the failure of two patients with the most highly penicillin-resistant strains was described, the only documented bacteriological failure occurred in a patient treated with ticarcillin, for which the MIC was 64 $\mu g \cdot mL^{-1}$. There was no bacteriological evidence of penicillin failure. Similar conclusions were reached in a retrospective study of nonmeningeal pneumococcal bacteremia in children in South Africa [12]. There was no difference in mortality between children infected with penicillin-resistant strains and those infected with susceptible strains. All children were treated with either intravenous ampicillin or penicillin, and a subsequent analysis revealed no difference in the time to resolution of symptoms or any other measure of morbidity between the two groups [13]. The majority of infections in both of these studies were intermediately resistant to penicillin [11, 12].

The pharmacokinetics of penicillin in serum have recently been reviewed by BRYAN *et al.* [14]. These data suggest that if a penicillin drug level exceeding the MIC of a resistant bacterium is required for 40% of the dosing interval, a penicillin dose of 2,000,000 units may be given 4-hourly to treat a highly resistant pneumococcus with an MIC of $\leqslant 4$ $\mu g \cdot mL^{-1}$ [15]. The same dose should be effective even if it is administered 6-hourly. Therefore, it may be concluded from pharmacodynamic principles that daily doses of intravenous penicillin in the range of 8–12 million $units \cdot day^{-1}$ should treat even highly-resistant pneumococcal infections.

Bacteriological evidence of the failure of β-lactam therapy in pneumonia

There are a number of reports on the failures of β-lactam agents for the management of penicillin-resistant pneumonia (table 1). The agents that failed are, in general, agents with less activity against the pneumococcus than penicillin or amoxicillin. Indeed, there are no reports of the bacteriological failure of either penicillin or amoxicillin, or of highly active agents such as the carbapenems, imipenem, or meropenem. Amongst the penicillins, the only case of bacteriological failure was the case previously described, of a patient treated with ticarcillin against a ticarcillin-resistant strain (MIC 64 $\mu g \cdot mL^{-1}$) [11]. The bacteriological failure of cefazolin, a first-generation cephalosporin, as well as the second-generation cephalosporin, cefuroxime, and the poorly active third-generation cephalosporin, ceftazidime, have all been described previously [16–19]. There is a single case report of a bacteriological failure of low dose cefotaxime ($100\ mg \cdot kg^{-1} \cdot day^{-1}$) plus gentamicin in a patient with a bacteremia caused by a highly resistant (cefotaxime MIC 6 $\mu g \cdot mL^{-1}$) pneumococcus [20]. This patient developed meningitis and the failure may have been due to seeding of organisms from the meninges to the blood.

Retrospective studies of β-lactam therapy for pneumonia

TURETT *et al.* [21] described an independent association of pneumococci with penicillin MICs of $\geqslant 2$ $\mu g \cdot mL^{-1}$ and mortality. This study did not adjust for severity of disease, and 50% of the patients were HIV infected. Indeed, only two patients in the study received penicillin. One patient infected with an intermediately resistant strain responded to oral amoxicillin, and the second patient, who was severely ill, infected with a highly-resistant strain, died after only a single dose of ticarcillin. This study therefore provides little evidence of the failure of β-lactam agents in the management of penicillin-resistant pneumococcal pneumonia.

Table 1. – Bacteriological failures of β-lactam therapy of respiratory tract infections caused by drug-resistant pneumococci

Therapeutic agent	Other drugs given	Site of growth of resistant bacterium	MIC of resistant bacterium $\mu g \cdot mL^{-1}$	Ref.
Ticarcillin		Blood	64	[11]
Cefazolin	Gentamicin	Blood	8	[16]
Cefuroxime	Clarithromycin Cefotaxime	Blood/CSF	8	[17]
Cefuroxime	Cefuroxime axetil Ceftriaxone Ceftibuten	Blood	8	[18]
Ceftazidime	Gentamicin	Blood	32	[19]

MIC: minimum inhibitory concentration; CSF: cerebrospinal fluid.

A retrospective analysis by FEIKEN *et al.* [22] revealed an intriguing association of late mortality (deaths after 4 days of therapy) in patients infected with pneumococci highly resistant to penicillin (MIC $\geqslant 4$ $\mu g \cdot mL^{-1}$). The odds ratio for mortality was 7.1 with a 95% confidence interval of 1.7–30. In the study, there was no association between penicillin MICs $\leqslant 2$ $\mu g \cdot mL^{-1}$ and mortality. While the late mortality may be suggestive of a true association between resistance and poor outcome, the authors were unable to stratify the data for severity of disease. It is also important to note that no information on antibiotic therapy was available to the authors, so that any association of resistance with mortality could not be related to the failure of specific antimicrobial agents [22]. In a retrospective chart review of 44 patients with penicillin nonsusceptible pneumococci (most of which were intermediate resistant), METLAY *et al.* [23] were unable to find an association of poor outcome with resistance once they controlled for severity of disease. The study did document an excess of suppurative complications (empyema); 2% (3 of 142) in patients infected with susceptible strains *versus* 9% (4 of 44) in patients with resistant strains. These data [20] suggest that resistant strains may be clinically nonresponsive to therapy in the setting of an empyema, an observation consistent with pharmacodynamic theory. MORONEY *et al.* [24] failed to find an association between cephalosporin strains with MICs $\geqslant 2$ and mortality. Poor outcome was related to severity of disease. A study in children in Uruguay, including a large number of children infected with highly penicillin-resistant strains, documented a failure rate based on clinical observation of 22% (5 of 23) in patients infected with the highly penicillin-resistant pneumococci [25]. This failure rate was high, but less than the 30% failure rate (17 of 52) found in patients infected with penicillin-susceptible *Streptococcus pneumoniae*. This study is important because the therapeutic choice was largely uninfluenced by the susceptibility results, as the susceptibility testing was performed on strains sent to Canada and the analysis of outcome was performed by an observer blinded to the resistance status of the pathogen. A recent analysis of 522 bacteremic episodes has documented no difference of 30-day mortality between patients infected with resistant and susceptible strains. The patients treated with penicillin or amoxicillin and infected with highly resistant strains had a 30-day mortality of 17% compared to 27% mortality in patients treated with intermediately resistant strains. A similar trend was observed in patients treated with cefotaxime or ceftriaxone, with 11% mortality amongst those infected with highly penicillin-resistant strains and 21% mortality in those with intermediately resistant strains [26]. These data suggest the possibility that more highly resistant strains may be less virulent. There are some data on experimental pneumonia in animals that support this contention [27].

Macrolides

In contrast to the lack of evidence of bacteriological failure in patients treated with active β-lactam drugs, there are now numerous case reports with bacteriological evidence of macrolide failure in patients infected with macrolide-resistant pneumococci (table 2). The following reports describe the culture from blood, or other sterile sites, of macrolide-resistant pneumococci from both children and adults receiving macrolide drugs. The first report was of a 2-yr-old male who developed pneumonia while receiving erythromycin. A pneumococcus with an erythromycin MIC of >8 $\mu g \cdot mL^{-1}$ was isolated from the patient's blood [28]. Two adults taking erythromycin with worsening pneumonia had lung aspirates that grew pneumococci and MICs of >8 $\mu g \cdot mL^{-1}$ [29]. A 32 yr old worsened on erythromycin therapy and the blood grew a pneumococcus with an MIC of 64 $\mu g \cdot mL^{-1}$ [30]. A 49-yr-old female deteriorated on azithromycin therapy and died despite addition of levofloxacin and vancomycin. A pneumococcus with an MIC of 16 $\mu g \cdot mL^{-1}$ grew from her blood [31]. Three patients being treated with azithromycin had pneumococci isolated from their blood. Their MICs were 8, 8, and >128 $\mu g \cdot mL^{-1}$, respectively [32]. Four patients, including one child, receiving azithromycin [3] or clarithromycin [1] had pneumococci isolated from their blood while they were receiving the drugs. Their erythromycin MICs were 8, 16, 16, and 8 $\mu g \cdot mL^{-1}$, respectively [33]. GARAU [34] has recently described a series of both adults and children in whom macrolide-resistant pneumococci were grown from blood while they were receiving macrolides or azithromycin therapy [34]. An analysis of these failures documents a threshold for bacteriological failure of ~ 8 $\mu g \cdot mL^{-1}$, a level unachievable for 50% of the dosing interval in patients treated with intravenous erythromycin. There has been some speculation as to whether the mechanism of macrolide resistance may lead to different outcomes in the management of macrolide-resistant pneumococcal pneumonia. Resistance mediated by the *ermB* gene leads to macrolide MICs usually in the range of >32 $\mu g \cdot mL^{-1}$, while macrolide resistance due to the *mefA* gene leads to variable expression of macrolide resistance in the range of 1–64 $\mu g \cdot mL^{-1}$. Recently, strains have been described that harbor both macrolide resistance mechanisms [35]. These strains are highly resistant to the macrolides (MICs of 128 $\mu g \cdot mL^{-1}$). As there have been bacteriologically documented failures in patients infected with pneumococci expressing *mefA* resistance when the MIC is $\geqslant 8$ $\mu g \cdot mL^{-1}$ [34], the level of MIC is, therefore, a more important predictor of the clinical relevance of macrolide resistance than is the presence of the *mefA* gene.

Trimethoprim-sulphamethoxazole

While this agent is rarely used for the management of pneumonia in developed countries, it remains the recommended drug of choice for the management of pneumonia in children in developing countries. This recommendation is based on the low cost of the agent and its activity against malaria in malaria endemic areas where the differential diagnosis of a child with pneumonia includes infection with *Plasmodium* sp. There are no data on the clinical relevance of

Table 2. – Bacteriological failures of macrolide therapy of respiratory tract infections caused by drug-resistant pneumococci

Therapeutic agent	Other drugs given	Site of growth of resistant bacterium	MIC of resistant bacterium $\mu g \cdot mL^{-1}$	Ref.
Erythromycin		Blood	>8	[28]
Erythromycin		Lung puncture	>8	[29]
Erythromycin		Lung puncture	>8	[29]
Erythromycin		Blood	>8	[30]
Erythromycin		Blood	>8	[34]
Erythromycin		Blood	>8	[34]
Erythromycin		Blood	>8	[34]
Azithromycin	Levofloxacin[#] Vancomycin	Blood	16	[31]
Azithromycin		Blood	8	[32]
Azithromycin		Blood	8	[32]
Azithromycin		Blood	>128	[32]
Azithromycin		Blood	8	[33]
Azithromycin		Blood	16	[33]
Azithromycin		Blood	16	[33]
Azithromycin		Blood	>8	[34]
Azithromycin		Blood	>8	[34]
Azithromycin		Blood	>8	[34]
Azithromycin		Blood	>8	[34]
Clarithromycin		Blood	8	[33]
Clarithromycin		Blood	>8	[34]
Clarithromycin		Blood	>8	[34]
Clarithromycin		Blood	>8	[34]
Josamycin		Blood	>8	[34]
Josamycin		Blood	>8	[34]

MIC: minimum inhibitory concentration. [#]: failed salvage therapy.

trimethoprim-sulphamethoxazole resistance for the management of pneumonia, although there are reports of the bacteriological failure of this agent in the management of pneumonia [28]. A randomised trial of trimethoprim-sulphamethoxazole *versus* amoxicillin in the management of pneumonia in Pakistan revealed a poorer outcome in the group receiving trimethoprim-sulphamethoxazole [36]. Although there was a high rate of resistance to this agent in the study, no consistent association of poor outcome with MIC could be established. Some data suggest that breakthrough bacteremias occur in human immunodeficiency virus (HIV)-infected patients receiving trimethoprim-sulphamethoxazole prophylaxis [37]. More data are required to document the impact of resistance to this agent on outcome, especially since widespread use of this agent may be expected in resource-poor countries in an attempt to prevent morbidity and mortality in HIV-infected adults and children, in the absence of therapy with effective antiretroviral agents.

Fluoroquinolones

There are bacteriologically confirmed failures of ciprofloxacin and, more recently, of levofloxacin, in the management of pneumococcal pneumonia, sinusitis, bronchitis, and exacerbation of chronic bronchitis (table 3) [38–43]. The pharmacodynamics of ciprofloxacin suggest that strains of pneumococci may not respond to therapy, even in the absence of resistance mutations. Once this and other fluoroquinolones,

Table 3. – Bacteriological failure of fluoroquinolone therapy of respiratory tract infections caused by drug-resistant pneumococci

Therapeutic agent	Initial infection	Other drugs given	Site of growth of resistant bacterium	MIC of resistant bacterium $\mu g \cdot mL^{-1}$	Ref.
Ciprofloxacin	Pneumonia		Empyema	4	[38]
Ciprofloxacin	AECB		Sputum	⩾8	[42]
Levofloxacin	Pneumonia		Sputum	8	[40]
Levofloxacin	Pneumonia		Sputum	16	[40]
Levofloxacin	AECB		Sputum	>32	[39]
Levofloxacin	Bronchitis		Sputum	>32	[41]
Levofloxacin	Pneumonia		Sputum	6	[43]
Levofloxacin[#]	Pneumonia		Sputum	⩾8	[42]
Levofloxacin[#]	AECB		Sputum	⩾8	[42]

MIC: minimum inhibitory concentration; AECB: acute exacerbation of chronic bronchitis. [#]: low dose 400 $mg \cdot day^{-1}$.

which are less active against the pneumococcus, have selected mutations in the *parC* or *gyrA* genes, therapy with pharmacodynamically more active agents such as levofloxacin may also fail. Indeed, the activity of levofloxacin against the pneumococcus is such that two mutations can lead to bacteriologically confirmed failures in patients infected with strains having MICs of $\geqslant 32\ \mu g \cdot mL^{-1}$. Two patients developed increasing resistance (MICs increasing from susceptible to 8 and from 4 to 16 $mg \cdot mL^{-1}$) to levofloxacin in isogenic strains from sputum, associated with treatment failure [40]. Seven further patients treated with ciprofloxacin or levofloxacin for pneumonia or exacerbations of chronic bronchitis failed clinically and had resistant strains isolated on therapy from the sputum [38, 39, 41–43].

At the present time, there is emerging fluoroquinolone resistance in Hong Kong, associated with widespread use of these agents for the management of pneumonia [44]. Although more active agents, such as gatifloxacin and moxifloxicin, may be used for the management of pneumonia, it is concerning that widespread use of less active fluoroquinolones for the treatment of pneumonia is confering resistance to the entire class of agents. To date, there have been no bacteriologically confirmed cases of failure of gatifloxacin or moxifloxicin in the management of pneumonia.

Other drugs

The failures of other drugs, such as the tetracyclines, streptogramins and rifamycins, have been documented when attempts were made to treat strains with MICs in excess of achievable blood levels [8, 10].

Conclusion

The global dissemination of antimicrobial resistance in the pneumococcus has lead to a number of therapeutic dilemmas in the management of pneumococcal pneumonia. Available evidence suggests that highly-active β-lactam agents, such as penicillin, amoxicillin, the extended-spectrum cephalosporins, cefotaxime or ceftriaxone, and the carbapenems, meropenem and imipenem, all retain useful clinical activity for the treatment of pneumococcal pneumonia. The vast majority of patients infected with penicillin-resistant pneumococci can be expected to respond to empirical therapy with these agents. Although no pneumococci resistant to vancomycin have been described, this agent should be reserved for combination therapy of meningitis, and there are few indications for its use in the management of pneumococcal pneumonia at this time. Patients not responsive to active β-lactam agents may be treated with fluoroquinolones with enhanced activity against the pneumococcus, such as gatifloxacin or moxifloxacin. While the macrolides have a clear role in combination empirical therapy of pneumonia, the widespread prevalence of macrolide resistance in the pneumococcus makes it difficult to justify empirical monotherapy with a macrolide. Empirical therapy of pneumonia with trimethoprim-sulphamethoxazole cannot be justified unless there are compelling financial reasons for its use. Pharmacodynamic principles have allowed the development of rational guidelines for the treatment of pneumonia. Optimal therapy depends on the selection of agents that are reliably able to kill pneumococci, even in an environment in which antibiotic-resistant strains are common.

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