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Augmentin® (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent

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Amoxicillin/clavulanate (Augmentin®) is a broad-spectrum antibacterial that has been available for clinical use in a wide range of indications for over 20 years and is now used primarily in the treatment of community-acquired respiratory tract infections. Amoxicillin/clavulanate was developed to provide a potent broad spectrum of antibacterial activity, coverage of β-lactamase-producing pathogens and a favourable pharmacokinetic/pharmacodynamic (PK/PD) profile. These factors have contributed to the high bacteriological and clinical efficacy of amoxicillin/clavulanate in respiratory tract infection over more than 20 years. This is against a background of increasing prevalence of antimicrobial resistance, notably the continued spread of β-lactamase-mediated resistance in *Haemophilus influenzae* and *Moraxella catarrhalis*, and penicillin, macrolide and quinolone resistance in *Streptococcus pneumoniae*. The low propensity of amoxicillin/clavulanate to select resistance mutations as well as a favourable PK/PD profile predictive of high bacteriological efficacy may account for the longevity of this combination in clinical use. However, in certain defined geographical areas, the emergence of *S. pneumoniae* strains with elevated penicillin MICs has been observed. In order to meet the need to treat drug-resistant *S. pneumoniae*, two new high-dose amoxicillin/clavulanate formulations have been developed. A pharmacokinetically enhanced tablet dosage form of amoxicillin/clavulanate 2000/125 mg twice daily (available as Augmentin XR® in the USA), has been developed for use in adult respiratory tract infection due to drug-resistant pathogens, such as *S. pneumoniae* with reduced susceptibility to penicillin, as well as β-lactamase-producing *H. influenzae* and *M. catarrhalis*. Amoxicillin/clavulanate 90/6.4 mg/kg/day in two divided doses (Augmentin ES-600®) is for paediatric use in persistent or recurrent acute otitis media where there are risk factors for the involvement of β-lactamase-producing strains or *S. pneumoniae* with reduced penicillin susceptibility. In addition to high efficacy, amoxicillin/clavulanate has a well known safety and tolerance profile based on its use in over 819 million patient courses worldwide. Reassuringly, the safety profiles of the two new high-dose formulations are not significantly different from those of conventional formulations. Amoxicillin/clavulanate is included in guidelines and recommendations for the treatment of bacterial sinusitis, acute otitis media, community-acquired pneumonia and acute exacerbations of chronic bronchitis. Amoxicillin/clavulanate continues to be an important agent in the treatment of community-acquired respiratory tract infections, both now and in the future.

Keywords: amoxicillin/clavulanate, respiratory tract infection, antimicrobial resistance, pharmacokinetics/pharmacodynamics, appropriate prescribing

Introduction

Amoxicillin/clavulanate (Augmentin‡) has been available for over 20 years, and continues to be one of the most widely used antibiotics available for clinical use, particularly in the treatment of respiratory tract infection. This paper explores the factors that led to the development of amoxicillin/clavulanate, the characteristics that have contributed to its continuing utility and the new enhancements that will sustain that utility in environments with increasing antimicrobial resistance.

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The discovery and development of amoxicillin/clavulanate

Penicillin to amoxicillin

The first clinically available antibiotic, benzyl penicillin (penicillin G), was identified and developed in the late 1920s and the 1930s, and came into clinical use during World War II. Despite rapid and widespread adoption of penicillin into clinical practice to satisfy an important unmet need, the agent was active against only a narrow range of bacteria, with clinically useful activity mainly against streptococci, staphylococci and gonococci. In addition, penicillin G was unsuitable for oral administration because of its instability to acid. In order to address these limitations, attempts were made to generate new therapeutic agents based on the penicillin molecule using different precursors in the fermentation process.[1] However, this process was capable of producing only limited structural diversity. A new approach that would greatly expand the range of compounds that could be produced and investigated was urgently required.

In the mid-1950s, investigators at Beecham Research Laboratories (BRL) identified the penicillin nucleus: 6-aminopenicillanic acid (6-APA).[1,2] The penicillin nucleus contains a β-lactam ring structure with no side chain. As yields of 6-APA from conventional fermentation were low, a new process of deacylation of a readily available penicillin was devised to produce the nucleus in larger quantities. This enabled research into the effects of adding various side chains and the generation of semi-synthetic penicillins. The primary objectives of this research were to develop oral penicillins with improved oral absorption, as well as molecules with broader spectra of activity. In addition, during the early 1940s, *Staphylococcus aureus* strains were identified that produced β-lactamase, an enzyme that inactivated the penicillins available at that time.[3] By 1948, half of the *S. aureus* strains in some hospitals, and 80% by 1957, were found to be resistant to penicillins.[2] Thus, the research effort was also directed at developing penicillins that were stable to *S. aureus* β-lactamase.[1] In 1959, phenethicillin was the first new penicillin launched as a result of this research programme, and had improved oral absorption compared with the natural penicillins G and V.[1] In 1960, a major breakthrough was achieved with methicillin.[1] This was the first β-lactam antibiotic stable to staphylococcal β-lactamase and was received as a 'life-saving' treatment for infections due to penicillin-resistant *S. aureus*, particularly in hospitals. Orally available penicillins stable to staphylococcal β-lactamase followed: notably cloxacillin and flucloxacillin.[1] Further research led to the important development of ampicillin, introduced in 1961, the first orally bioavailable broad-spectrum penicillin with activity against Gram-negative organisms such as *Haemophilus influenzae*, *Escherichia coli* and *Salmonella typhi*.[1] BRL continued to produce many different semi-synthetic agents, and a single change to the side chain of ampicillin resulted in amoxicillin (introduced in 1972).[1] Amoxicillin had the same potent broad-spectrum activity as ampicillin, but with much better oral absorption, giving blood concentrations approximately twice as high as those obtained with ampicillin.[1,2] In addition, amoxicillin showed more rapid bactericidal activity against certain pathogens compared with ampicillin.[1,2]

β-Lactamase, clavulanate and amoxicillin/clavulanate

Production of β-lactamase in Gram-negative bacteria was described in 1940 in *E. coli*.[4] In the 1960s, β-lactamase produced by Gram-negative bacteria was found to be different from the staphylococcal type, being located intracellularly and thus able to act against the β-lactam agents on their entry into the bacterium. The development of ampicillin and then amoxicillin, with their extended antimicrobial activity against Gram-negative organisms, meant that β-lactamase production in these organisms became an important clinical issue. In addition, the ability to produce β-lactamase was found to be transferable between *E. coli* and other species via plasmids during cell-to-cell contact, raising the possibility of transfer to species not previously known to produce β-lactamase.[5] Although different penicillins had been developed with good oral absorption, extended antibacterial spectra and stability to β-lactamase, an agent possessing all three of these qualities was lacking.

It was known that cloxacillin, flucloxacillin and other β-lactamase-stable β-lactams competitively inhibit β-lactamase, but these agents were not potent enough against the desired range of target enzymes to sufficiently protect the broad-spectrum penicillins. Eventually, after a specific screening programme by BRL, a β-lactam molecule produced by *Streptomyces clavuligerus* was discovered and found to be a potent inhibitor of β-lactamases, but with low antibacterial activity; this molecule was named clavulanic acid.[1,6] The β-lactam ring of clavulanic acid irreversibly binds to the bacterial β-lactamase, thus inhibiting the enzyme and preventing it from binding to and inactivating β-lactam antibiotics.[7] Clavulanate has some effects on pathogenic bacteria regardless of β-lactamase production, although their clinical significance has not been established.[8]

The β-lactamase-inhibiting properties of clavulanic acid[9] were combined with the good oral absorption and potent broad-spectrum antimicrobial activity of amoxicillin[1,10] in tablets containing amoxicillin trihydrate and potassium clavulanate. In this form, amoxicillin/clavulanate was first launched as Augmentin in the UK in 1981,[10] and subsequently throughout the world. Paediatric formulations and an intravenous formulation followed, and are now also available in many countries worldwide.

Amoxicillin/clavulanate today

Indications for amoxicillin/clavulanate. Amoxicillin/clavulanate was originally developed in response to the need for an oral broad-spectrum antibiotic that covered β-lactamase-producing pathogens. Amoxicillin/clavulanate retained the good activity of amoxicillin against β-lactamase-negative strains, restored its activity against β-lactamase-producing strains, such as in *S. aureus*, *E. coli* and *H. influenzae*, and extended its activity against *Klebsiella pneumoniae* and the anaerobic *Bacteroides fragilis* (most strains of the latter produce β-lactamase).[10–12] Early studies demonstrated the efficacy of amoxicillin/clavulanate in infections caused by β-lactamase-producing pathogens in urinary, respiratory and soft tissue sites,[13–19] and in diseases such as gonorrhoea and chancroid.[20,21]

Amoxicillin/clavulanate is now most commonly used in the empirical treatment of bacterial respiratory tract infections, such as community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), acute bacterial rhinosinusitis (ABS) and acute otitis media (AOM). The main bacterial pathogens implicated in community-acquired lower respiratory tract infection (CAP and AECB) and AOM are *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*.[22,23] These three organisms are also associated with bacterial sinusitis in children, but only *S. pneumoniae* and *H. influenzae* are commonly isolated from adults with bacterial sinusitis.[24,25] Anaerobes are also believed to be important pathogens in sinusitis and recurrent tonsillitis.[25,26]

Recent data indicate that clinical success rates for amoxicillin/clavulanate in respiratory tract infection and AOM are maintained at ~90%.[27–31] Amoxicillin/clavulanate is therefore a valuable treatment for respiratory tract infections, in particular because the physician is often unable to determine the underlying causative pathogen(s) in such infections, and thus empirical therapy is required. At the end of 2002, amoxicillin/clavulanate was clinically available as various formulations in over 150 countries around the world.

Optimized dosage development of amoxicillin/clavulanate based on pharmacokinetics/pharmacodynamics (PK/PD)

Amoxicillin/clavulanate formulations

Initially, the adult formulation of amoxicillin/clavulanate was introduced as Augmentin at a three times daily dose of 250 mg of amoxicillin (as amoxicillin trihydrate) plus 125 mg of clavulanic acid (as potassium clavulanate).[10] Over the years, the ratio of amoxicillin to clavulanate has been varied to reflect prescribing needs, to improve convenience and as a response to recommendations for the treatment of more severe infections or those caused by resistant organisms. However, within the majority of oral formulations, the unit dose of clavulanate has remained as 125 mg for adults and 3.2 mg/kg for paediatrics (250–375 mg and 6.4–10 mg/kg daily dose), this amount being sufficient to inhibit the clinically relevant target β-lactamases and protect the amoxicillin component.[11]

To reflect local standard amoxicillin dosages, a 500/125 mg (4:1) three times daily amoxicillin/clavulanate regimen was registered in continental Europe (first in Germany, in 1982) and the USA (in 1986).

In order to treat more severe disease, 875/125 mg three times daily (Spain and Italy) or 1000/125 mg (8:1) three times daily (France) adult regimens were introduced.

Twice daily formulations of 500/125 mg and 875/125 mg are now available in many countries, and offer increased convenience and patient compliance over the three times daily regimens, along with efficacy comparable to the 250/125 mg three times daily or 500/125 mg three times daily formulations, respectively.[32] The adult 875/125 mg (7:1) twice daily formulation was launched in the USA and other countries from the mid-1990s.

In order to combat drug-resistant *S. pneumoniae*, a high-dose adult 2000/125 mg twice daily formulation has been developed with an extended-release amoxicillin component that enhances the pharmacokinetics of this formulation and allows coverage of more bacterial strains than conventional dosing.[33] The high-dose pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg formulation has become available recently in the USA (as Augmentin XR‡) for the treatment of CAP or ABS due to β-lactamase-producing bacteria (e.g. *H. influenzae* or *M. catarrhalis*) or *S. pneumoniae* with reduced susceptibility to penicillin (penicillin MICs ≤ 2 mg/L). This formulation is also approved in some European countries with various indications in respiratory tract infection, including CAP, ABS and AECB.

The paediatric amoxicillin/clavulanate 4:1 ratio three times daily dosage regimens (20/5 and 40/10 mg/kg/day) are now registered widely throughout the world. In order to improve convenience, twice daily formulations were introduced in the latter half of the 1990s in many countries.[34–36] The standard paediatric dosage of amoxicillin/clavulanate for the treatment of mild to moderate infections in many countries is now 25/3.6 mg/kg/day (in two divided doses).

For more severe infections, such as AOM, the dose can be increased up to 45/6.4 mg/kg/day (in two divided doses). In some European countries, in order to be in line with prescribing guidelines for amoxicillin in severe infections, formulations are available providing up to 80/10 mg/kg/day in three divided doses (France, Spain, and children under 2 years in Belgium and The Netherlands) or 70/10 mg/kg/day in two divided doses (Germany, Austria, Switzerland and Portugal).

Drug-resistant *S. pneumoniae* is usually more prevalent in children than in adults and can be difficult to treat with the standard antimicrobials.[23] In order to address this issue, a new high-strength 90/6.4 mg/kg/day paediatric suspension formulation given as two divided doses (Augmentin ES-600‡) has become available in the USA for the treatment of recurrent AOM due to *S. pneumoniae* (penicillin MICs ≤ 2 mg/L), *H. influenzae* (including β-lactamase-producing strains) or *M. catarrhalis* (including β-lactamase-producing strains) characterized by antibiotic exposure for AOM within the preceding 3 months, and either age ≤2 years or day-care attendance.[37] The availability of this formulation will be extended to other countries.

The standard intravenous dose of amoxicillin/clavulanate is 1000/200 mg administered every 8 h, although higher doses of 2000/200 mg are used when indicated.[38]

Pharmacokinetics of amoxicillin/clavulanate

Amoxicillin and clavulanate are both well absorbed from the gastrointestinal tract, reaching peak serum levels 60–90 min and 40–120 min, respectively, after separate oral administration.[39] Combining the two drugs does not affect their pharmacokinetics.[40] A single dose of 250/125 mg of amoxicillin/clavulanate produces a mean peak concentration of 4.2 mg/L for amoxicillin and 2.6 mg/L for clavulanic acid.[15] The mean peak concentrations of amoxicillin after single doses of 500/125 and 875/125 mg amoxicillin/clavulanate are 7.2 and 11.6 mg/L, respectively (data on file, GlaxoSmithKline). Amoxicillin has an approximately linear dose–response over the range 250–2000 mg.[41,42] The penetration of amoxicillin into respiratory tract secretions is greater than, for example, ampicillin, despite similar peak serum concentrations,[43] as demonstrated by the significantly higher levels of amoxicillin than ampicillin in the sputum of subjects receiving both drugs intravenously. Studies with amoxicillin/clavulanate have shown that the sputum levels of clavulanate are comparable to those of amoxicillin, taking into account the relative difference in the two doses.[41,44]

The elimination half-lives of amoxicillin and clavulanate are similar: 63 min for a 500 mg dose of amoxicillin and 60 min for a 125 mg dose of clavulanate in healthy volunteers.[45,46] Amoxicillin is excreted in the urine mostly unmetabolized, and 50–85% is found in the urine 6 h after an oral dose.[47] Clavulanate, on the other hand, is appreciably metabolized and the products are excreted via faeces, urine and lungs.[48] Six hours after an oral dose, 20–60% of the clavulanate dose appears unchanged in urine.[49]

Pharmacodynamic rationale for amoxicillin/clavulanate dosage development

Maximizing bacterial eradication is a key goal in the selection of appropriate antimicrobial therapy in respiratory tract infection.[50,51] Bacteriological eradication is important not only to ensure clinical success but also to reduce the potential for the development and spread of resistance.[50–52] The bacteriological efficacy of antimicrobials is dependent on their PK/PD properties.[53,54] For β-lactam agents,

the bacteriological efficacy is particularly dependent on the time that free serum concentrations of the drug exceed the MIC for the target pathogen ($T > MIC$).[54–56] For amoxicillin, a $T > MIC$ of 30–40% of the dosing interval is required for maximal bacteriological efficacy against the key respiratory pathogen *S. pneumoniae* in animal infection models.[54,57] The magnitude of the PK/PD index required for maximal eradication is thought to be similar for *H. influenzae*.[54,58] For β-lactams, particularly those with linear pharmacokinetic dose responses, increases in pathogen MICs can be overcome with increased unit doses, dose frequency and/or improved pharmacokinetics to maintain adequate $T > MIC$.[59–61] In contrast, for the macrolides, limitations in pharmacokinetics and safety prevent dosages being increased or modified sufficiently to overcome macrolide-resistant *S. pneumoniae* or to confer *in vivo* bacteriological efficacy against *H. influenzae*.[61] The bacteriological efficacy of fluoroquinolones is concentration dependent. Thus, in order to increase efficacy, there is a need to increase the total amount of drug given per dose.[61] Fluoroquinolones have a relatively narrow safety window, limiting the doses that can be given, and most agents would not be able to maintain an acceptable safety/tolerability profile and overcome quinolone resistance in *S. pneumoniae*.[61] As a consequence, PK/PD modification to overcome resistance is largely unfeasible for macrolides and fluoroquinolones, and requires the development of new, more active molecules.[60,61]

Table 1 shows the steady-state mean $T > MIC$ for the different formulations of amoxicillin/clavulanate for different pathogen MICs (data on file, GlaxoSmithKline).[33,60–64] Based on PK/PD predictions, amoxicillin/clavulanate 875/125 mg twice daily would achieve maximal bacteriological efficacy against strains with amoxicillin or amoxicillin/clavulanic acid MICs of ≤2 mg/L but not ≥4 mg/L, although the 875/125 mg three times daily and 1000/125 mg three times daily regimens would be expected to have some efficacy against strains with MICs of 4 mg/L.

A new pharmacokinetically enhanced adult tablet formulation of amoxicillin/clavulanate 2000/125 mg twice daily has been developed to maximize PK/PD against strains with elevated penicillin and amoxicillin MICs. Amoxicillin/clavulanate 2000/125 mg is given as two 1000/62.5 mg tablets, taken twice daily. The enhanced pharmacokinetics of this formulation are achieved by using a novel bilayer design of tablet, providing a total dose of 1125 mg of amoxicillin trihydrate plus 125 mg of clavulanate potassium, both as standard-release forms, plus an extended-release component of 875 mg of crystalline sodium amoxicillin.[33]

The pharmacokinetics of the clavulanate component of the new formulation are the same as for the conventional amoxicillin/clavulanate formulations, which contain the same unit dose of 125 mg sufficient to inhibit the target β-lactamases.[11,33] Figure 1(a) compares the pharmacokinetics of the new immediate- plus sustained-release amoxicillin component of the 2000/125 mg formulation with the normal 875 mg conventional dose of amoxicillin.[33,57] The extension in the $T > MIC$ can be seen clearly. In addition, a comparison of the new formulation with 2000 mg of immediate-release amoxicillin, in a subset of seven patients, illustrates the contribution of the sustained-release technology to the improvement in pharmacokinetics (Figure 1b).[33] The sustained-release component flattens the concentration curve, increasing the time for which amoxicillin serum concentrations are maintained above 4 mg/L, while maintaining the C_{max} at a value higher than that of the 875 mg dose, but lower than that obtained with 2000 mg of immediate-release amoxicillin.

The effect of the inclusion of an extended-release component in the new 2000/125 mg twice daily formulation can be seen clearly in Table 1.[33] Against pathogens with amoxicillin MICs of 4 mg/L, amoxicillin/clavulanate 2000/125 mg twice daily achieves a mean $T > MIC$ of 49% of the dosing interval, and for pathogens with amoxicillin MICs of 8 mg/L a $T > MIC$ of 35%.[33]

Table 1. PK/PD parameters for selected amoxicillin/clavulanate formulations (data on file, GlaxoSmithKline)[33,60–64]

Amoxicillin/clavulanate formulation (ratio)	Dosing regimen	Amoxicillin C_{max} (mg/L)	Mean $T > MIC$ for amoxicillin (% of dosing interval) for MICs (mg/L) of:			
			1	2	4	8
250/125 mg (2:1)	three times daily	3.3	40	–	–	–
500/125 mg (4:1)	three times daily	7.2	55	43	–	–
875/125 mg (7:1)	twice daily	11.6	44	40	–	–
875/125 mg (7:1)	three times daily	11.6	69	57	34	–
1000/125 mg[a] (8:1)	three times daily	12.5	>65	55	41	–
2000/125 mg[b] (16:1)	twice daily	17.0	>70	60	49	35
Paediatric formulations (data shown for suspensions)						
125/31.25 or 250/62.5 mg/5 mL (4:1)	40/10 mg/kg/day (three divided doses)	6.5	59	44	–	–
200/28.5 or 400/57 mg/5 mL (7:1)	45/6.4 mg/kg/day (two divided doses)	10.9	50	41	–	–
600/42.9 mg/5 mL (14:1)	90/6.4 mg/kg/day (two divided doses)	15.8	61	50	41	–

–, $T > MIC \leq 30\%$.
[a]Available in France only.
[b]Extended-release tablets.

A high-dose paediatric suspension (Augmentin ES-600; amoxicillin/clavulanate 90/6.4 mg/kg/day) has been introduced in the USA, where it is approved in a regimen of two divided doses. This reflects a need for a potent antimicrobial for the treatment of recurrent or persistent AOM, a difficult-to-treat infection, where there are risk factors for the involvement of antimicrobial-resistant pathogens. Table 1 shows that, based on pharmacodynamic predictions, amoxicillin/clavulanate 90/6.4 mg/kg/day should be effective against bacterial strains with elevated penicillin and amoxicillin MICs.[60,65]

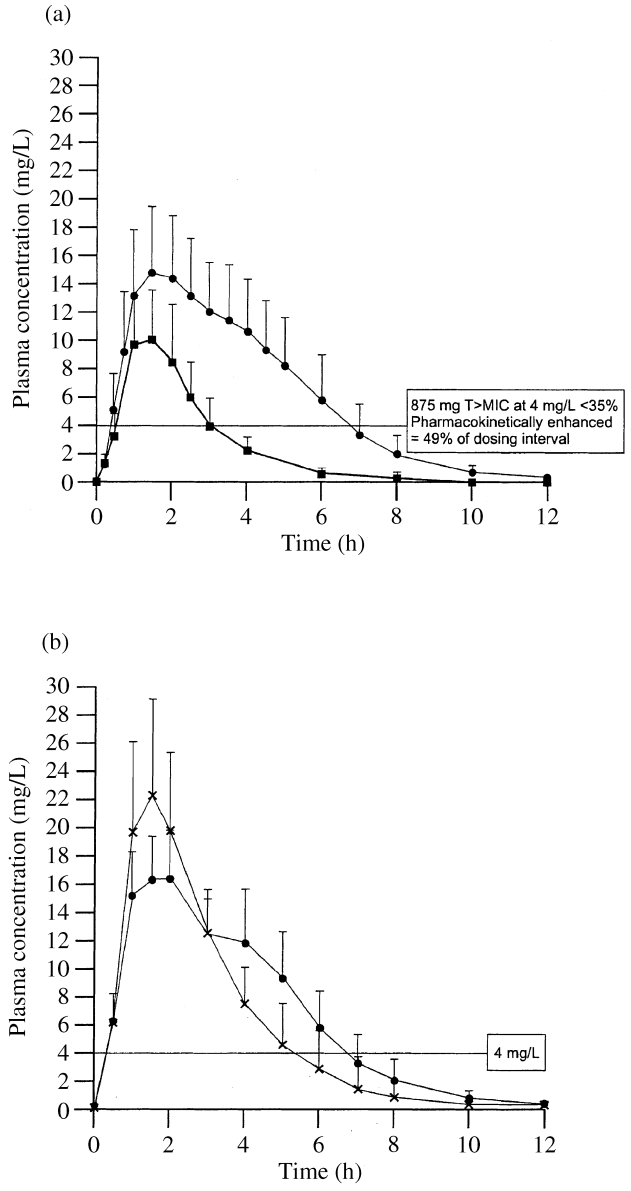

Figure 1. Mean plasma concentration–time profile for amoxicillin after oral administration of (a) pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg ($n = 55$) (filled circles) compared with 875/125 mg of conventional release amoxicillin/clavulanate ($n = 14$) (filled squares).[33,57] (b) Pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg ($n = 7$) (filled circles) compared with 2000 mg of conventional immediate-release amoxicillin ($n = 7$) (crosses).[33] Part (b) reproduced with permission.[33]

Bacteriological efficacy of optimized doses in in vitro and in vivo models

Both the adult 2000/125 mg formulation and the paediatric 90/6.4 mg/kg/day suspension were developed using PK/PD predictions for the eradication of drug-resistant bacterial strains based on data from animal models and from clinical studies in AOM.[54,60,61,65] Confirmation of their predicted bacteriological efficacy against strains of *S. pneumoniae* with elevated amoxicillin MICs has been obtained from *in vitro* and *in vivo* models.[66–69] For example, the antibacterial effect of pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg twice daily was compared with that of the standard 875/125 mg twice daily formulation in an *in vitro* pharmacokinetic model of *S. pneumoniae* infection.[66] Against six *S. pneumoniae* strains with amoxicillin MICs of 3–8 mg/L, the $T >$ MIC for the 2000/125 mg twice daily formulation was 39–61% compared with 20–41% for the standard 875/125 mg twice daily formulation. The 2000/125 mg formulation would therefore be expected to have a greater antibacterial effect (i.e. smaller area under the bacterial killing curve) than the 875/125 mg formulation against the strains with higher amoxicillin MICs. Figure 2 shows the area under the bacterial killing curve for the two formulations at 12 and 24 h after addition of a bacterial inoculum of 10^6 cfu/mL. Even by 12 h after inoculation, for amoxicillin MICs > 4 mg/L, the 2000/125 mg formulation is more active than the standard formulation (Figure 2a).[66] By 24 h, there is very little difference in the antibacterial effect of 2000/125 mg across the different strains, indicating that activity has been retained even against strains with amoxicillin MICs of 8 mg/L. In contrast, the antibacterial effect of the 875/125 mg formulation is variable above

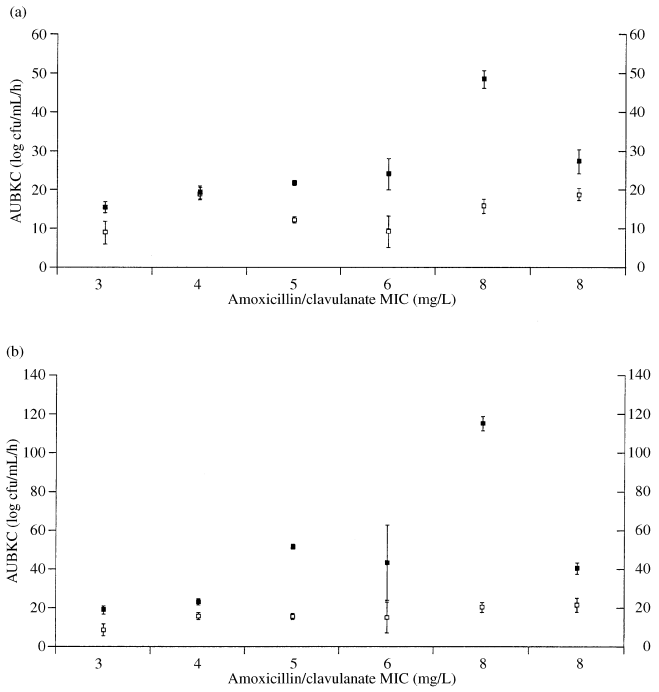

Figure 2. Area under the bacterial killing curve (AUBKC; lower values indicate increased antibacterial effect) for amoxicillin/clavulanate 2000/125 mg twice daily (open squares) and amoxicillin/clavulanate 875/125 mg twice daily (filled squares) in an *in vitro* pharmacodynamic model (a) 12 h after inoculation and (b) 24 h after inoculation against six strains of *S. pneumoniae*. Adapted with permission.[66]

amoxicillin MICs of 4 mg/L and is less active than the 2000/125 mg formulation against these strains (Figure 2b).[66] Similarly, an *in vitro* model simulating pharmacokinetics in humans demonstrated that increased amoxicillin doses are more effective than lower doses against penicillin non-susceptible *S. pneumoniae*, and dosages equivalent to 70–90 mg/kg/day provided adequate coverage of these strains.[67]

The effect of the increased $T >$ MIC for amoxicillin/clavulanate 2000/125 mg was investigated in a rat model of respiratory tract infection in which human pharmacokinetics were simulated.[68] Dosing in the rat approximating the PK/PD in humans of amoxicillin/clavulanate 2000/125 mg twice daily was compared with that of amoxicillin/clavulanate 1000/125 mg three times daily, 875/125 mg three times daily, and 875/125 mg twice daily, against *S. pneumoniae* strains with amoxicillin MICs of 4 or 8 mg/L.[68] Table 1 indicates that, based on PK/PD predictions, the 875/125 mg twice daily formulation would have insufficient efficacy against strains with amoxicillin MICs of 4 mg/L, and that only the pharmacokinetically enhanced 2000/125 mg twice daily formulation would be effective against strains with MICs of 8 mg/L. In this model, a mean reduction in bacterial count of ~3 logs indicates maximal bacteriological efficacy. Figure 3 shows bacterial killing plotted against the $T >$ MIC for the four different amoxicillin/clavulanate formulations. There is a clear distinction above a $T >$ MIC of ~35% between maximal bacterial killing and insufficient killing.[68] As predicted based on PK/PD, the 875/125 mg twice daily formulation was ineffective against *S. pneumoniae* with amoxicillin MICs of 4 mg/L and 8 mg/L; the 875/125 mg three times daily and 1000/125 mg three times daily formulations were effective against strains with MICs of 4 mg/L but not 8 mg/L; and amoxicillin/clavulanate 2000/125 mg twice daily was effective against strains with MICs of 4 mg/L and 8 mg/L, and superior to the other formulations tested against *S. pneumoniae* with amoxicillin MICs of 8 mg/L.[68] Amoxicillin/clavulanate 2000/125 mg twice daily was also significantly more effective than azithromycin against four macrolide-resistant strains, two with azithromycin MICs of 4 mg/L and two with MICs of >32 mg/L.[68] Interestingly, amoxicillin/clavulanate 2000/125 mg twice daily was significantly more effective than levofloxacin 500 mg once daily against all three of the strains with amoxicillin MICs of 4 mg/L and one of the strains with an amoxicillin MIC of 8 mg/L ($P < 0.01$), even though all of the strains were susceptible to levofloxacin (levofloxacin MICs 0.5–1 mg/L).[68]

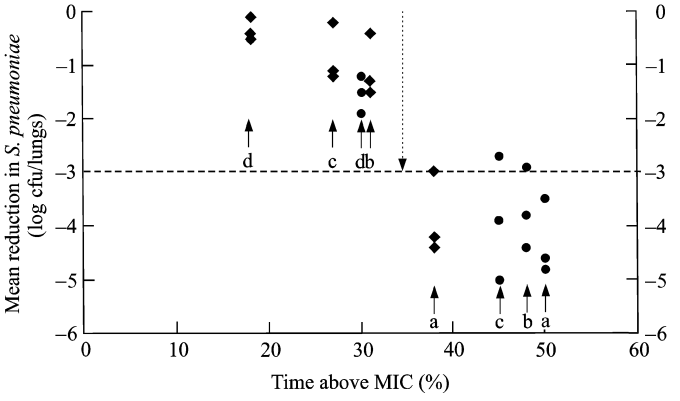

Figure 3. $T >$ MIC for amoxicillin/clavulanate dosed in a rat respiratory tract infection model to simulate human dosing with the following formulations (a) 2000/125 mg twice daily; (b) 1000/125 mg three times daily; (c) 875/125 mg three times daily; and (d) 875/125 mg twice daily, and degree of reduction in bacterial load against three strains of *S. pneumoniae* with amoxicillin/clavulanate MICs of 4 mg/L (filled circles) and three strains with amoxicillin/clavulanate MICs of 8 mg/L (filled diamonds).[68] The broken arrow indicates the cut off for maximal efficacy (~3 log reduction) at a $T >$ MIC of ~35%.

The efficacy of dosing equivalent to 45/6.4 mg/kg/day amoxicillin/clavulanate or 90/6.4 mg/kg/day amoxicillin/clavulanate has also been studied in this rat respiratory tract infection model against penicillin-resistant *S. pneumoniae* strains with amoxicillin MICs of 2, 4 or 8 mg/L.[69] Both doses were effective against the strain with a MIC of 2 mg/L, but only the higher dose was effective against the strain with an MIC of 4 mg/L.[69] Neither dose was effective against the strain with an MIC of 8 mg/L. These results are consistent with those predicted based on PK/PD parameters, with efficacy being maintained where the $T >$ MIC was at least 34% (Table 1).[58,60,69]

These studies indicate the value of using PK/PD in the optimization of current antibacterials in order to overcome existing resistance and to maintain bacteriological efficacy as resistance increases.[60,61,65]

Maintaining the clinical and bacteriological efficacy of amoxicillin/clavulanate in a resistance environment

The prevalence of antimicrobial resistance in respiratory tract pathogens has been increasing in many areas of the world and threatens to undermine the efficacy of some commonly prescribed antimicrobials.[59,70–72] A review of clinical failures due to antimicrobial resistance could not find any published cases of failures of penicillin therapy in respiratory tract infection due to penicillin-resistant *S. pneumoniae* when adequate doses have been used.[59] However, there have been several reports of bacteriologically proven failures in patients receiving other classes of agent.[59,70,73–75] Clinical failures in CAP due to erythromycin-resistant *S. pneumoniae* have been documented in patients receiving therapy with macrolides,[59,70,73] as has the on-therapy emergence of macrolide-resistant strains.[74] In addition, several reports of clinical failures in CAP with levofloxacin against *S. pneumoniae* have been published,[59,75] including the emergence of resistance on-therapy.[75] This has been attributed to the suboptimal PK/PD profile for levofloxacin against *S. pneumoniae* at the 500 mg/day dose, which allows the *in vivo* emergence of resistant strains at subinhibitory concentrations.[59,75]

Maintaining bacteriological efficacy in a resistance environment is dependent upon achieving PK/PD targets predictive of bacteriological eradication. Established and new agents, or the optimization of existing therapies, should be evaluated on this basis rather than on clinical trials that are designed to show only equivalence of clinical cure between agents.[50,51,76]

M. catarrhalis and H. influenzae

Amoxicillin/clavulanate was originally developed to extend the antibacterial spectrum of amoxicillin to include β-lactamase-producing species.[1] Over the 20 years or more in which amoxicillin/clavulanate has been available, this property has become increasingly important as the prevalence of β-lactamase production has increased in many countries. In bacterial isolates collected in 2001 as part of the Alexander Project, β-lactamase production in *H. influenzae* was 10–20% in isolates from Switzerland, Spain, Russia and the UK, and 20–>30% in Hong Kong, the USA, Saudi Arabia, Singapore and France (Figure 4; Alexander Project; data on file, GlaxoSmithKline); β-lactamase production in *M. catarrhalis* in 2001 ranged from 88.9% in Germany to 100% in France and Hong Kong. The prevalence of β-lactamase-

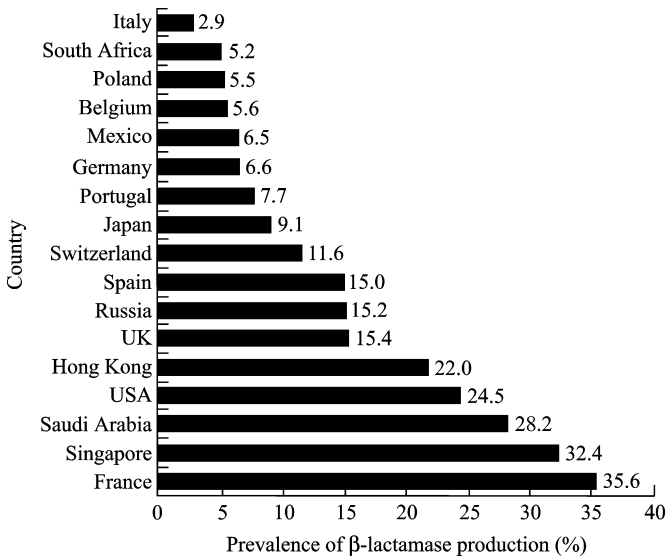

Figure 4. Prevalence of β-lactamase production in *H. influenzae* (n = 2240) in 2001 (Alexander Project; data on file, GlaxoSmithKline).

negative ampicillin-resistant *H. influenzae* strains (BLNAR; ampicillin MICs ≥ 4 mg/L) remains low worldwide. In the 2001 Alexander Project, 14/2240 (0.6%) strains collected worldwide were BLNAR; 11 from Japan, one from Saudi Arabia and two from the USA. No β-lactamase-positive amoxicillin/clavulanate-resistant *H. influenzae* strains (BLPACR) were collected in 2001 (Alexander Project; data on file, GlaxoSmithKline).

The worldwide susceptibility of *H. influenzae* according to PK/PD breakpoints for amoxicillin (≤2 mg/L) and amoxicillin/clavulanate for the conventional formulations (≤2 mg/L) and high-dose formulations (2000/125 mg twice daily, adult, and 90/6.4 mg/kg/day, paediatric; ≤4 mg/L) has been studied in the Alexander Project (Alexander Project; data on file, GlaxoSmithKline). Susceptibility to amoxicillin varied between 78% and 86% between 1992 and 2001, and mirrored the prevalence of β-lactamase production (83% in 2001; MIC_{50} 0.5 mg/L, MIC_{90} >16 mg/L, MIC range 0.12–>16 mg/L). The susceptibility of *H. influenzae* to conventional formulations of amoxicillin/clavulanate was >97% over this period, although the high-dose formulations would have provided additional coverage, with >99% of isolates susceptible (98% and 100% in 2001, respectively; MIC_{50} 0.5 mg/L, MIC_{90} 1 mg/L, MIC range 0.12–16 mg/L). For *M. catarrhalis*, although 94% of isolates were β-lactamase producers in 2001, the susceptibility of this organism to conventional amoxicillin/clavulanate was 99%, with 100% of isolates susceptible to the high-dose formulations (MIC_{50} 0.12 mg/L, MIC_{90} 0.25 mg/L, MIC range 0.12–4 mg/L). These results illustrate the maintained effective role of clavulanate in protecting amoxicillin from β-lactamase production in *H. influenzae* and *M. catarrhalis*.

Bacteriological efficacy of amoxicillin/clavulanate against H. influenzae and M. catarrhalis. The efficacy of standard doses of amoxicillin/clavulanate against *H. influenzae* in comparison with amoxicillin and macrolides has been demonstrated in a rat pneumonia model using antimicrobial concentration profiles equivalent to those achieved in human serum. After 3 days of therapy against a β-lactamase-positive strain of *H. influenzae*, amoxicillin/clavulanate (equivalent human dose amoxicillin/clavulanate 500/125 mg twice daily) was significantly more effective at reducing bacterial numbers than amoxicillin (500 mg twice daily) ($P \leq 0.01$).[77] Amoxicillin/clavulanate was also significantly superior to erythromycin (equivalent human dose 500 mg three times daily), and clarithromycin given at a dose equivalent to either 250 or 500 mg twice daily ($P < 0.01$).[77] Bacterial numbers following treatment with either dose of clarithromycin used in this study were not significantly different to controls ($P > 0.05$).[77] In a similar experiment, using the same *H. influenzae* strain, amoxicillin/clavulanate was compared with amoxicillin and azithromycin.[77] Again, amoxicillin was ineffective, with similar results to the untreated controls ($P > 0.05$). Azithromycin (equivalent to 500 mg once daily) did reduce bacterial numbers significantly compared with controls, but was not as effective as amoxicillin/clavulanate.[77]

These results are supported by clinical evidence from human studies in AOM. Double tympanocentesis allows comparison of the normally aseptic middle ear fluid before and after antimicrobial treatment. Thus, the antibacterial effect of antimicrobial therapy can be assessed accurately.[50,52] Amoxicillin/clavulanate (45/6.4 mg/kg/day in two divided doses for 10 days) was compared with azithromycin (10 mg/kg on day 1 then 5 mg/kg/day for 4 days) in a single-blind study of 238 infants and children with AOM.[78] After 4–6 days of treatment, in evaluable patients who were culture positive for *H. influenzae* as a single pathogen at screening, 26/30 (86.7%) in the amoxicillin/clavulanate group had achieved bacteriological success, compared with 13/33 (39.4%) in the azithromycin group ($P = 0.0001$).[78] The higher bacteriological efficacy of amoxicillin/clavulanate also resulted in significantly higher clinical efficacy against *H. influenzae* at day 12–14 ($P = 0.01$) (Figure 5).[78] In this study, amoxicillin/clavulanate also demonstrated a 100% bacteriological success rate against *M. catarrhalis* (no *M. catarrhalis* was identified in the azithromycin group).[78]

Evidence of the efficacy of amoxicillin/clavulanate against *H. influenzae* is also available in AECB. In an open randomized trial of amoxicillin/clavulanate (875/125 mg twice daily for 8 days) versus azithromycin (500 mg once daily for 3 days) in AECB, 15 patients in the amoxicillin/clavulanate group and 26 in the azithromycin group had *H. influenzae* isolated from sputum at the start of therapy.[79] At the end of therapy (10 days after therapy start),

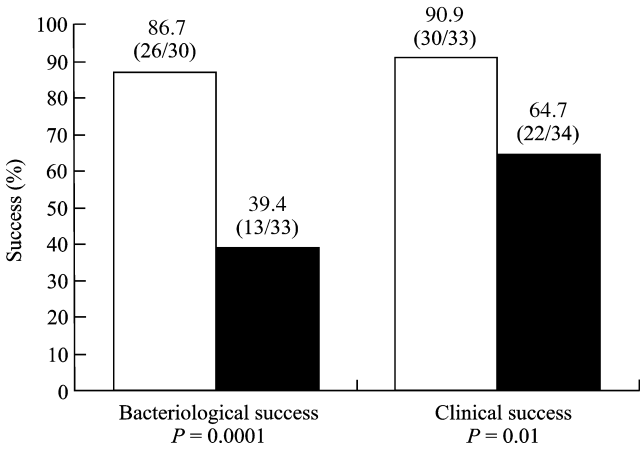

Figure 5. Amoxicillin/clavulanate 45/6.4 mg/kg/day in two divided doses (white bars) bacteriological success after 4–6 days of therapy and clinical success at day 12–14 versus azithromycin 10 mg/kg/day for day 1, then 5 mg/kg/day for days 2–5 (black bars) against *H. influenzae* in AOM.[78]

H. influenzae was undetectable in the sputum in all of the patients who had received amoxicillin/clavulanate, whereas in the azithromycin group *H. influenzae* persisted in 13 patients (50.0%).[79]

These data from animal studies and clinical trials in AOM and AECB support the continued high efficacy of amoxicillin/clavulanate against *H. influenzae* and *M. catarrhalis*, including β-lactamase-producing strains. In contrast, the poorer PK/PD profile of the macrolides may explain the lower rates of bacteriological eradication in these studies.[52]

Efficacy of high-dose formulations against H. influenzae. Although conventional formulations of amoxicillin/clavulanate are highly clinically and bacteriologically effective against *H. influenzae*, there is still potential to maximize outcomes with the high-dose formulations. Evidence for this comes from *in vitro* and *in vivo* models, as well as clinical studies in AECB and AOM.[37,80–83]

Löwdin *et al.*[80] studied the pharmacodynamics of amoxicillin/clavulanate 2000/125 mg twice daily in an *in vitro* pharmacokinetic model compared with the 875/125 mg twice daily and 500/125 mg three times daily formulations. In this model, bacterial killing with these formulations was assessed at 4 h intervals for a total of 24 h against four clinical strains and one laboratory test strain of *H. influenzae*, all β-lactamase producers. Although both of the standard formulations resulted in significant bacterial killing (3–4 log change in cfu/mL), the 2000/125 mg pharmacokinetically enhanced formulation was significantly more effective against the *H. influenzae* strains at 8, 16 and 24 h ($P < 0.01$) versus the standard twice daily regimen, and at 8 and 16 h versus the 500/125 three times daily regimen ($P < 0.01$).[80]

The 2000/125 mg twice daily formulation has also been tested against *H. influenzae* in a rat respiratory tract infection model in which doses that simulate human pharmacokinetics were used.[81] In this study, a BLNAR *H. influenzae* strain with an amoxicillin/clavulanic acid MIC of 4 mg/L was used. Against this strain, amoxicillin/clavulanate 2000/125 mg twice daily was significantly more effective than the standard 875/125 twice daily formulation and azithromycin (azithromycin MIC 2 mg/L) ($P \leq 0.01$).[81] Against a second β-lactamase-positive strain, with an amoxicillin/clavulanic acid MIC of 1 mg/L, amoxicillin/clavulanate 2000/125 mg twice daily was at least as effective as the other formulations tested, indicating that the proportion of clavulanate is sufficient to protect the extended amoxicillin concentrations to achieve efficacy.[81] In a clinical study of amoxicillin/clavulanate 2000/125 mg in AECB, bacteriological presumed efficacy (eradication of a pathogen identified at baseline at the follow-up visit, or clinical cure in a patient with confirmed bacteriological infection at baseline in the absence of a microbiologically evaluable sample at follow-up) against *H. influenzae* was 86.2% (25/29) compared with 75.0% (24/32) for the 875/125 mg formulation (*P* value not calculated as this was not a pre-specified comparison).[82]

A study of high-dose amoxicillin/clavulanate (90/6.4 mg/kg/day) in AOM indicated that this formulation was highly effective against *H. influenzae*, eradicating the pathogen in 78/83 (94.0%) of patients after 4–6 days.[37] In comparison, a similar study of the conventional 45/6.4 mg/kg/day dose resulted in a bacteriological eradication rate of 76.9% (30/39) (Figure 6).[78] This is significantly lower than that obtained with the high-dose formulation ($P = 0.01$).[65] Similarly, in a comparative study, high-dose amoxicillin/clavulanate eradicated 89.7% (35/39) of *H. influenzae* at day 4–6 compared with 49.1% (27/55) eradication for azithromycin ($P < 0.001$).[83]

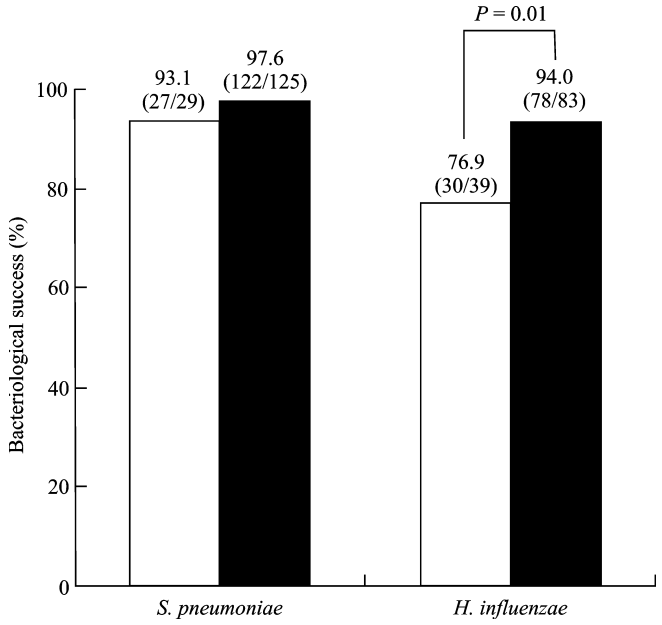

Figure 6. Bacteriological success of amoxicillin/clavulanate 45/6.4 mg/kg/day in two divided doses (white bars) after 4–6 days of therapy *versus* amoxicillin/clavulanate 90/6.4 mg/kg/day (black bars) against *S. pneumoniae* and *H. influenzae* in AOM.[37,78]

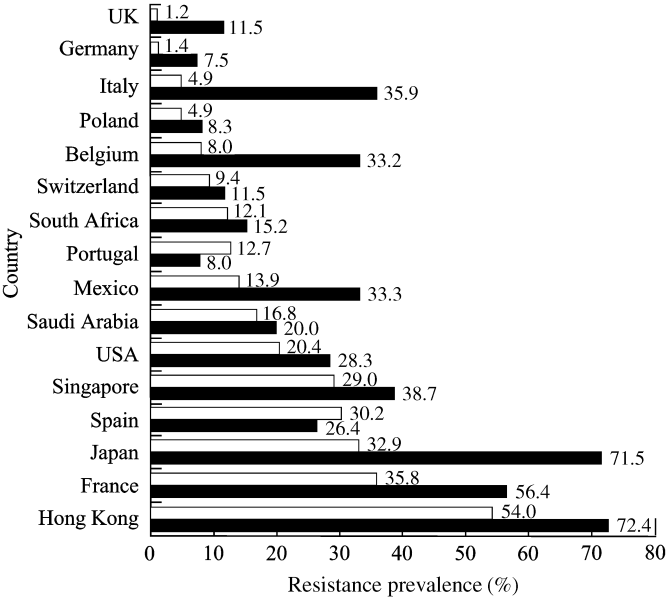

Figure 7. Prevalence (%) of penicillin- (MIC ≥ 2 mg/L) (white bars) and erythromycin-resistant (MIC ≥ 1 mg/L) (black bars) *S. pneumoniae* ($n = 2482$) in 2001 (Alexander Project; data on file, GlaxoSmithKline).

S. pneumoniae

The development and spread of penicillin, macrolide and now also fluoroquinolone resistance in *S. pneumoniae* is of particular concern.[59,72,84,85] In the Alexander Project in 2001, 10/16 countries had a prevalence of penicillin resistance and 13/16 had a prevalence of

macrolide resistance that exceeded 10% (Figure 7; penicillin MIC_{50} 0.03 mg/L, MIC_{90} 2 mg/L, MIC range ≤0.015–8 mg/L; erythromycin MIC_{50} 0.06 mg/L, MIC_{90} >32 mg/L, MIC range ≤0.015–>32 mg/L; Alexander Project; data on file, GlaxoSmithKline). The prevalence of macrolide resistance exceeded that of penicillin resistance in 14 of the 16 countries. *S. pneumoniae* is the most common pathogen isolated in respiratory tract infection, and the development of clones resistant to multiple classes of antimicrobial agent provides a therapeutic challenge.[23,86]

Consistently high prevalences of penicillin resistance in *S. pneumoniae* strains have been recorded by the Alexander Project between 1992 and 2001 (10–24% overall, although prevalences vary greatly between countries) (Alexander Project; data on file, GlaxoSmithKline).[71] Based on PK/PD and current NCCLS breakpoints (≤2 mg/L),[72,87] the overall susceptibility of *S. pneumoniae* collected as part of the 2001 Alexander Project to amoxicillin/clavulanate was 96.1%, whereas susceptibility to the high-dose formulations using the PK/PD breakpoint of ≤4 mg/L was 98.1% (MIC_{50} 0.03 mg/L, MIC_{90} 2 mg/L, MIC range ≤0.015–16 mg/L) (Alexander Project; data on file, GlaxoSmithKline). Although this difference may appear small, the high-dose formulations provide increased reassurance in infections where resistant strains may be involved.[33,50,51,67] In addition, the use of high-dose formulations may reduce the potential for the emergence and spread of resistance.[50] This is particularly valuable in countries that currently have low resistance prevalences.[50] The difference between the high-dose versus conventional formulations is more noticeable when just the penicillin-non-susceptible strains collected in 2001 are examined; 94.3% of these strains were susceptible to amoxicillin/clavulanate using the ≥4 mg/L PK/PD breakpoint versus 88.4% when using the ≥2 mg/L breakpoint (MIC_{50} 1 mg/L, MIC_{90} 4 mg/L, MIC range ≤0.015–16 mg/L).[84] Also, when resistance prevalences increase, the difference in susceptibility between conventional formulations and high-dose amoxicillin/clavulanate also increases. For example, Alexander Project data from the USA in 1992 recorded a prevalence of penicillin-resistant *S. pneumoniae* of 5.6%; the susceptibility of all *S. pneumoniae* isolated to standard amoxicillin/clavulanate (breakpoint ≤2 mg/L) was 98.4%, and would have been 100% to the high-dose formulations (using a PK/PD breakpoint ≤4 mg/L) (MIC_{50} ≤0.06 mg/L, MIC_{90} 0.25 mg/L, MIC range ≤0.06–4 mg/L).[88] In 2001, 20.4% of *S. pneumoniae* isolates were resistant to penicillin in the USA; the susceptibility to standard amoxicillin/clavulanate had become 91.1%, with 98.5% of strains susceptible to the high-dose formulations (based on breakpoints of ≤2 and ≤4 mg/L, respectively; MIC_{50} 0.03 mg/L, MIC_{90} 2 mg/L, MIC range ≤0.015–16 mg/L) (Alexander Project; data on file, GlaxoSmithKline).

Penicillin-resistant strains of *S. pneumoniae* with amoxicillin ± clavulanic acid MICs ≥ 4 mg/L are a significant problem in certain resistance 'hot spots'. The countries with *S. pneumoniae* strains with amoxicillin/clavulanic acid MICs ≥ 2 mg/L isolated in the 2001 Alexander Project are shown in Table 2 (Alexander Project; data on file, GlaxoSmithKline). Strains with amoxicillin/clavulanic acid MICs ≤ 2 mg/L are susceptible to conventional formulations of amoxicillin/clavulanate. For strains with amoxicillin/clavulanic acid MICs ≥ 4 mg/L, all were non-susceptible to penicillin (95/96 isolates penicillin resistant and one intermediate) and non-susceptible to other oral β-lactams. Owing to the high prevalence of cross-resistance between penicillin and macrolides in most countries,[72] these isolates are also likely to be non-susceptible to macrolides; 75% (339/451) of penicillin-resistant *S. pneumoniae* were also resistant to erythromycin in the 2001 Alexander Project. In addition, 62/96 (65%) of *S. pneumoniae* strains with amoxicillin/clavulanic acid MICs ≥ 4 mg/L were resistant to erythromycin. Fluoroquinolone non-susceptibility is still uncommon in *S. pneumoniae*.[72] However, in Hong Kong in 2001, 32% of penicillin-resistant strains were also quinolone resistant (based on an ofloxacin MIC of ≥8 mg/L;[87] MIC_{50} 2 mg/L, MIC_{90} >8 mg/L, MIC range 1–>8 mg/L). Thus, the options for treating infections caused by penicillin-resistant *S. pneumoniae* with amoxicillin/clavulanic acid MICs of ≥4 mg/L are limited using conventional formulations of amoxicillin/clavulanate or other antimicrobials, including quinolones in certain regions.

Table 2. Prevalence of *S. pneumoniae* strains with amoxicillin/clavulanic acid MICs ≥ 2 mg/L in 2001 (Alexander Project; data on file, GlaxoSmithKline)

Country	Total isolates	Isolates (%) with amoxicillin/clavulanic acid MICs (mg/L): 2	4	8	16
Belgium	187	7.0	0.5	–	–
France	165	26.7	1.8	1.2	–
Germany	147	0.7	–	–	–
Hong Kong	87	36.8	6.9	–	–
Italy	103	3.9	1.0	–	–
Japan	228	22.4	–	–	–
Mexico	72	16.7	–	–	–
Poland	144	4.9	–	–	–
Portugal	213	7.0	1.4	1.9	0.5
Saudi Arabia	95	5.3	7.4	–	–
Singapore	62	19.4	–	–	–
South Africa	99	9.1	1.0	1.0	–
Spain	106	17.0	2.8	5.7	4.7
Switzerland	139	5.0	2.2	–	–
UK	87	1.2	–	–	–
USA	548	11.9	3.8	4.4	0.7

–, no strains at this MIC.

Bacteriological efficacy of amoxicillin/clavulanate against S. pneumoniae. Animal experiments indicate that amoxicillin/clavulanate is bacteriologically effective against many penicillin-non-susceptible *S. pneumoniae* strains. For example, in a rat model of pneumonia, doses equivalent to amoxicillin/clavulanate 500/125 mg three times daily and 875/125 mg twice daily were tested against a penicillin-resistant strain of *S. pneumoniae* (MIC 2 mg/L for penicillin and amoxicillin/clavulanic acid).[57] Both doses significantly reduced bacterial numbers in the lungs compared with controls ($P < 0.01$).

The effect of increasing penicillin MICs on bacteriological efficacy can be seen in double tympanocentesis studies in AOM. In a study of 188 patients, amoxicillin 50 mg/kg/day was compared with cefaclor 40 mg/kg/day.[89] Against *S. pneumoniae* strains with penicillin MICs < 0.1 mg/L, there were no therapy failures in the amoxicillin therapy group (0/10), compared with three out of 16 (18.8%) in the cefaclor group. However, in strains with penicillin MICs ≥ 2 mg/L, four out of 14 (28.6%) patients in the amoxicillin arm had bacteriological failure compared with 11/17 (64.7%) in the cefaclor arm.[89] This difference can be explained using PK/PD parameters: serum levels of amoxicillin remain above the bacterial MIC for a longer period than can be achieved for cefaclor. Effectively, this results in

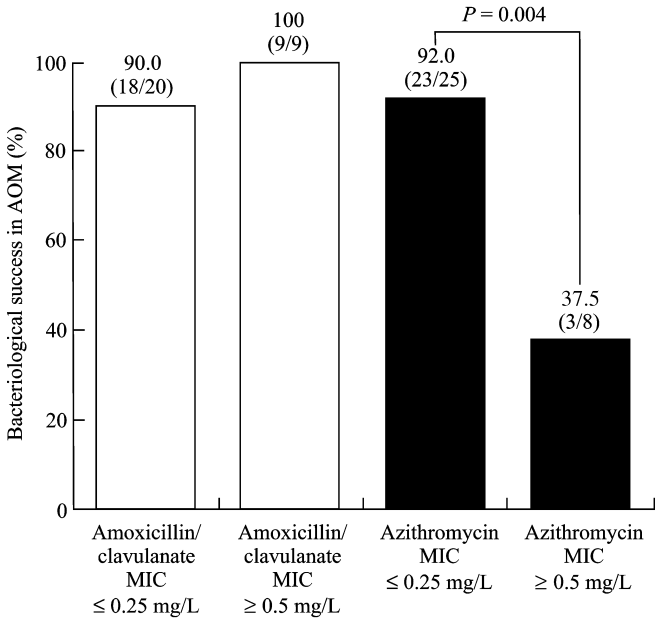

Figure 8. Effect of elevated penicillin and macrolide MICs on the bacteriological success of amoxicillin/clavulanate (white bars) and azithromycin (black bars) in AOM.[74] Reproduced with permission.[59]

cefaclor having a four-fold lower PK/PD breakpoint than amoxicillin. Thus, the cefaclor MIC that will compromise cefaclor bacteriological efficacy will be lower than the amoxicillin MIC that would result in reduced efficacy of amoxicillin. In a further study in AOM, penicillin susceptibilities ranging between ≤0.25 and >2 mg/L had no effect on amoxicillin/clavulanate bacteriological efficacy against *S. pneumoniae*.[78] In contrast, macrolide MICs ≥ 0.5 mg/L significantly compromised the efficacy of azithromycin against this pathogen ($P = 0.004$) (Figure 8).[78]

These studies suggest that conventional amoxicillin/clavulanate remains highly effective against *S. pneumoniae*, including some penicillin-non-susceptible strains and macrolide-resistant strains. However, the new high-dose formulations provide additional assurance in areas or patients where strains with elevated penicillin MICs may be suspected.

Efficacy of high-dose formulations against drug-resistant S. pneumoniae. A combined analysis of clinical data in respiratory tract infection (CAP, AECB and ABS) showed that the presumed bacteriological efficacy of amoxicillin/clavulanate 2000/125 mg twice daily was 94.6% (506/535) in patients with *S. pneumoniae* identified at baseline (bacteriology per-protocol population at follow-up).[90] Against penicillin-resistant *S. pneumoniae* (MICs ≥ 2 mg/L), amoxicillin/clavulanate 2000/125 mg twice daily achieved presumed bacteriological success in 50/52 patients (96.2%). In addition, amoxicillin/clavulanate 2000/125 mg twice daily was presumed bacteriologically effective against six out of seven *S. pneumoniae* isolates with amoxicillin MICs of 4 mg/L, and against seven out of eight strains with amoxicillin MICs of 8 mg/L. All 15 strains with amoxicillin MICs of 4–8 mg/L were penicillin resistant.[90] These results for the pharmacokinetically enhanced formulation of amoxicillin/clavulanate 2000/125 mg twice daily are in line with the high bacteriological efficacy against penicillin-resistant pneumococci predicted using PK/PD parameters.[61,90] In patients with CAP, presumed bacteriological efficacy of amoxicillin/clavulanate 2000/125 mg was 92.9% (276/297) against *S. pneumoniae* and 96.0% (24/25) against penicillin-resistant strains.[91] In acute bacterial sinusitis, amoxicillin/clavulanate 2000/125 mg achieved presumed bacteriological success in 96.3% (207/215) of patients with *S. pneumoniae* and 95.7% (22/23) of patients with penicillin-resistant strains.[91,92]

These results indicate the potential benefit of amoxicillin/clavulanate 2000/125 mg twice daily in the treatment of respiratory tract infections where the involvement of drug-resistant *S. pneumoniae* is suspected or where β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* are a concern. In addition, the safety and tolerability profile of the 2000/125 mg twice daily formulation is comparable to that of conventional formulations in clinical trials.[82,93–95]

The paediatric suspension of amoxicillin/clavulanate 90/6.4 mg/kg/day was developed to address a particular need in recurrent or persistent AOM due to *S. pneumoniae* with reduced susceptibility to penicillin or β-lactamase-producing *H. influenzae* or *M. catarrhalis*. High efficacy of this formulation against penicillin-resistant strains was shown in a non-comparative clinical study of amoxicillin/clavulanate 90/6.4 mg/kg/day, in two divided doses, in children with AOM.[37] At baseline, the most common pathogen isolated from children who had a second tympanocentesis at day 4–6 was *S. pneumoniae* (122/222) followed by *H. influenzae* (58/222), or both of these pathogens (37/222). After 4–6 days of amoxicillin/clavulanate 90/6.4 mg/kg/day therapy, a repeat tympanocentesis showed eradication of 97.6% (122/125) of *S. pneumoniae* (Figure 6).[37] This included many strains with elevated penicillin MICs, with 87/87 penicillin-susceptible (MIC ≤ 0.6 mg/L), one out of one penicillin-intermediate (MIC 1 mg/L) and 31/34 penicillin-resistant (MIC 2–4 mg/L) *S. pneumoniae* strains eradicated with the high-dose therapy (MICs were unavailable for three pathogens).[37] Overall, 95.6% (172/180) of all pathogens were eradicated from the bacteriologically evaluable patients. In a recent comparative trial, amoxicillin/clavulanate 90/6.4 mg/kg/day eradicated 96.0% (72/75) of *S. pneumoniae* compared with 80.4% (74/92) eradication with azithromycin ($P < 0.01$).[83] In this study, amoxicillin/clavulanate eradicated 92.0% (23/25) of penicillin-resistant *S. pneumoniae* versus 54.5% (12/22) eradication with azithromycin ($P < 0.01$).[83] These studies indicate that amoxicillin/clavulanate 90/6.4 mg/kg/day offers effective therapy for recurrent or persistent AOM due to strains of *S. pneumoniae* with reduced penicillin susceptibility, as well as providing coverage of β-lactamase-producing *H. influenzae* or *M. catarrhalis.*[37,83] An evaluation of amoxicillin/clavulanate 90/6.4 mg/kg/day versus the standard paediatric unit dose of amoxicillin/clavulanate 45/6.4 mg/kg/day showed both formulations to be generally well tolerated, with no significant differences in the adverse event profile between the two groups.[96]

Amoxicillin/clavulanate and the potential for the development and spread of resistance

In vitro selection of resistance

Resistance to β-lactam antimicrobials in *S. pneumoniae* is primarily due to changes in the penicillin-binding proteins (PBPs), leading to a reduced affinity to these agents.[97] These changes are brought about by the recombination of genes from other streptococcal species and native genes to create mosaic PBPs.[98]

β-Lactams vary in their ability to select for spontaneously resistant mutants in the native genes of susceptible *S. pneumoniae* strains, or for increased resistance in strains already harbouring resistance

mutations in mosaic genes. These differences are investigated in mutation selection experiments, which have shown differences between the penicillins (including amoxicillin ± clavulanic acid) and various cephalosporins in their potential to select resistant bacterial strains.[99,100] Penicillins appeared to have relatively low frequencies of selection for one-step mutants, which were cross-resistant to the cephalosporins and which had small increases in MIC. In contrast, for some of the cephalosporins tested (cefixime, cefuroxime, cefpodoxime, ceftriaxone, cefotaxime[99] and cefaclor[100]), higher rates of selection were seen along with different resistance profiles and relatively large increases in MICs, although the MICs of the penicillins for these strains remained low or actually decreased.[99,100] These laboratory studies suggest that penicillins, such as amoxicillin ± clavulanate may have a lower potential than certain cephalosporins for the selection of resistance in pneumococci.

Resistance to macrolides and fluoroquinolones is acquired through different mechanisms to those underlying penicillin resistance. However, macrolide and fluoroquinolone resistance can also be selected for by exposure to subinhibitory antimicrobial concentrations to these agents. Resistance selection with amoxicillin ± clavulanic acid was compared with azithromycin by Pankuch *et al.*[100] Subculturing with amoxicillin/clavulanic acid produced an increased MIC in only one out of six penicillin-susceptible strains (the amoxicillin MIC increased from 0.008 to 0.125 mg/L), and MICs remained stable in all of the four penicillin-intermediate isolates tested.[100] In comparison, azithromycin readily selected resistant strains, with eight out of 10 strains displaying increased azithromycin MICs (increased from 0.03–4 to 0.5–>256 mg/L).[100] For the quinolones, Davies *et al.*[101] found that ciprofloxacin, grepafloxacin, sparfloxacin and levofloxacin selected for increased MICs in all 10 strains of *S. pneumoniae* tested, and trovafloxacin in eight of 10 strains, with all strains exhibiting at least an eight-fold increase in MIC for at least three of these five agents. In contrast, subculturing in amoxicillin/clavulanic acid at subinhibitory concentrations led to an increase in MIC for only one out of 10 strains after 24 subcultures (from 0.015 to 0.125 mg/L).[101] These studies indicate that amoxicillin/clavulanate has a lower potential for the *in vitro* selection of resistant *S. pneumoniae* strains than azithromycin or various quinolones.

Similar multi-step selection studies have also been performed for resistance selection in *H. influenzae*, indicating that amoxicillin/clavulanate or cefpodoxime did not lead to the development of resistant strains, although the cefpodoxime MICs for some strains did increase to a level similar to that seen in β-lactamase-negative ampicillin-resistant strains.[102] MICs of another cephalosporin, cefprozil, increased in one β-lactamase-negative strain. In contrast, the macrolides azithromycin and clarithromycin readily selected for resistant *H. influenzae* strains (azithromycin 10/10 strains, clarithromycin eight out of 10 strains), with very high MICs (≥256 mg/L to either azithromycin or clarithromycin) in six out of 10 strains.[102]

The mutation studies described above indicate the potential to develop resistance to fixed antibiotic concentrations *in vitro*. Other factors, such as antimicrobial concentrations at the site of infection, duration of exposure to subinhibitory concentrations and inherent potency and bactericidal activity of the agent against the pathogen (i.e. PK/PD parameters), as well as the presence of multi-resistant pathogens, clonal spread and the biological cost of resistance to the organism, all play a role in resistance development and spread in the clinical situation.[103]

In vitro PK/PD modelling of resistance

The effect of PK/PD parameters on the development of resistance was investigated by Thorburn *et al.*[104] in an *in vitro* pharmacodynamic model simulating antimicrobial human serum concentrations after oral twice daily dosing. Against a penicillin-resistant strain of *S. pneumoniae*, cefpodoxime 200 mg was ineffective ($T >$ MIC of 0% for the 12 h dosing period), while cefuroxime 500 mg showed initial bactericidal activity, although the cultures regrew between doses ($T >$ MIC of 25%).[104] Amoxicillin 500 mg, with a $T >$ MIC of 29%, was bactericidal against this strain at 6 h post-dose, but there was some regrowth by 24 h, whereas amoxicillin/clavulanate 875/125 mg, with a $T >$ MIC of 42%, was rapidly bactericidal, reducing bacterial levels to the limit of detection at 48 h and with no regrowth up to 54 h (the end of the experiment).[104] Suboptimal PK/PD parameters and bacterial regrowth with cefpodoxime and cefuroxime were associated with the emergence of strains that had a four- to eight-fold increase in the MIC of cefpodoxime and an eight-fold increase in the MIC of cefuroxime compared with isolates from an untreated control culture. These isolates showed cross-resistance with cefotaxime, but not penicillin G or amoxicillin/clavulanate. In contrast, isolates from cultures exposed to either amoxicillin or amoxicillin/clavulanate showed no change in their susceptibilities to penicillin G or cephalosporins.[104]

Mathematical modelling has also been used to predict the impact of different PK/PD profiles on resistance. For example, a model using different concentrations of amoxicillin versus cefixime in a population of *S. pneumoniae* with a mixed resistance profile showed that even at low concentrations (0.12 and 0.25 mg/L), amoxicillin tended to select for low- rather than high-level resistance.[105] At a higher concentration (0.5 mg/L), repeated challenges with amoxicillin led to the exclusion of resistant strains. In comparison, cefixime tended to select for high-level resistance at all concentrations.[105]

For oral cephalosporins, bacteriological efficacy requires a $T >$ MIC of at least 40% (compared with 30–40% for penicillins).[55] An analysis of Alexander Project data compared with data on prescribing habits suggested that an increase in penicillin-resistant *S. pneumoniae* in France corresponded to an increased proportional use of oral cephalosporins that failed to achieve this PK/PD target, and facilitated the spread of a few resistant clones.[106] Similarly, the propensity of the newer macrolides to select resistance is thought to be related to the long half-lives of these agents.[24,107] For example, azithromycin has a half-life of 68 h, meaning that total elimination from the body does not occur until 14–20 days after dosing. During this time, serum concentrations will be below the MIC, providing a 'selection window' for the development of resistant strains.[24,105,107] An analysis of surveillance data from the Alexander Project compared with prescribing data found that there was a high correlation between macrolide resistance in *S. pneumoniae* and the use of newer, longer-acting macrolides, such as azithromycin and clarithromycin ($r = 0.896$), but no correlation with the older, short-acting macrolides ($r = -0.099$).[107]

Bacterial eradication and resistance

Dagan *et al.*[50] postulated that failure to eradicate the infecting organisms can lead to the development of resistant clones, which then recolonize the mucosal membranes after the discontinuation of antibacterial therapy. Consequently, the absolute number of resistant populations will increase and the within-host proliferation is then followed by transmission of the resistant clones to other hosts. This leads to a negative spiral in which resistant clones spread, making

bacterial eradication more difficult, leading to further spread of the clone.[50]

The use of antimicrobial agents that have PK/PD profiles predictive of bacterial eradication not only maximizes the potential to eliminate colonizing or infecting bacteria, but also minimizes the exposure of bacterial pathogens to subinhibitory concentrations, which could lead to the selection of resistant members of bacterial populations.[50,51,70,73] The use of agents with optimized PK/PD allows the additional potential benefit of eradication of organisms resistant to other agents or doses.[50,51,60]

Nasopharyngeal carriage

The nasopharynx acts as an important reservoir of bacterial infection.[50] In order to minimize the spread of pathogens, including resistant strains, antimicrobial therapy should aim to maximize bacterial eradication at both the site of infection and in the nasopharynx.[50]

An open-label, randomized, multicentre study in 501 infants (6–36 months of age) with AOM compared the impact of treatment with either cefixime suspension, 8 mg/kg/day in two divided doses, or amoxicillin/clavulanate suspension, 80/10 mg/kg/day in three divided doses, for 10 days on the nasopharyngeal carriage of *S. pneumoniae* and *H. influenzae*. Nasopharyngeal swabs were obtained at enrolment, at the end of treatment and at follow-up on day 35. At the end of therapy, the number of children carrying either penicillin-susceptible or -resistant *S. pneumoniae* was significantly lower in the amoxicillin/clavulanate group than in the cefixime-treated children.[108]

The effect of increasing the dose of amoxicillin and reducing the therapy duration on nasopharyngeal carriage was examined by Schrag *et al.*[109] In this study, children aged 6–59 months with respiratory tract illness were given 90 mg/kg/day for 5 days (n = 398) or 40 mg/kg/day for 10 days (n = 397) as two divided doses. Twenty-eight days after therapy was initiated, the carriage of penicillin-non-susceptible *S. pneumoniae* was significantly lower in the short-course, high-dose group (24%) compared with the standard-course group (32%; $P = 0.01$). Adherence to treatment was also higher in the short-course, high-dose group (82%) compared with the comparator group (74%; $P = 0.02$) (Figure 9).[109]

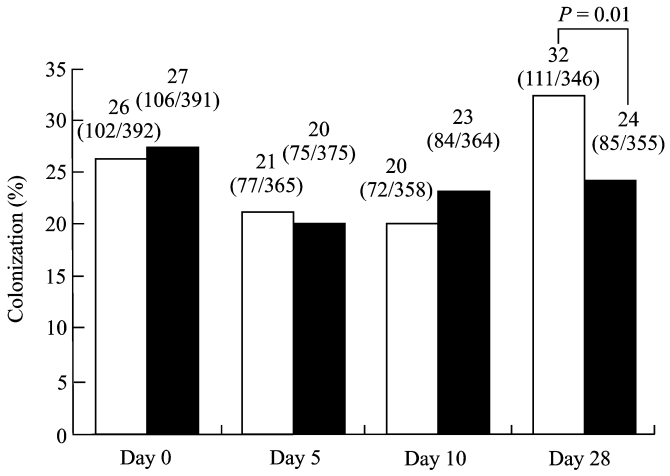

Figure 9. Nasopharyngeal colonization with penicillin-non-susceptible *S. pneumoniae* after treatment of respiratory tract infection with either amoxicillin 40 mg/kg/day for 10 days (white bars) or 90 mg/kg/day for 5 days (black bars).[109]

The effect of high-dose amoxicillin/clavulanate 90/6.4 mg/kg/day (in two divided doses for 10 days) on nasopharyngeal carriage in children with AOM has also been compared with azithromycin 10 mg/kg/day (once on the first day then 5 mg/kg/day for 4 days).[110] The group receiving amoxicillin/clavulanate 90/6.4 mg/kg/day had a significant decrease in the carriage of *S. pneumoniae* and *H. influenzae* 2 weeks after the initiation of therapy ($P < 0.001$ and $P = 0.005$, respectively). In contrast, there was no significant difference in the rate of carriage at 2 weeks in the azithromycin group.[110] At first glance, the results of Schrag *et al.*, showing the protective effect of short-dose amoxicillin therapy, may appear to be in conflict with the results for short-course azithromycin in this study. However, as azithromycin cleared only 69% of azithromycin-susceptible strains of *S. pneumoniae* and 29% of azithromycin-resistant strains, it is likely that concentrations of this agent were too low to achieve effective bacterial therapy.[110] These findings indicate the importance of achieving a balance between dose and duration while maintaining PK/PD targets predictive of bacterial eradication.[103] Similarly, in a comparative study, in the presence of penicillin-resistant and multi-drug-resistant *S. pneumoniae*, azithromycin (10 mg/kg for 1 day, 5 mg/kg for 4 days) rapidly promoted carriage of penicillin- and multi-resistant strains, whereas high-dose amoxicillin/clavulanate (90 mg/kg/day for 10 days) had a minimal effect on the carriage of these strains.[111] The difference in the carriage of resistant strains between the two groups was maintained for at least 1 month.[111]

Within the clinical setting, failure to eradicate bacteria from the infection site and the nasopharynx facilitates the emergence and subsequent spread of resistant clones of *S. pneumoniae* and *H. influenzae* throughout the population.[50] The potential to eradicate both antimicrobial-susceptible and -resistant isolates is therefore a key consideration in the choice of therapy.[50,51]

Safety profile

Amoxicillin/clavulanate is generally well tolerated. The largest analysis of amoxicillin/clavulanate safety and tolerability was performed by Neu *et al.*[93] They examined safety data from 374 mutually exclusive reports of amoxicillin/clavulanate clinical trials published between 1979 and 1992, including 32 440 patients. All of these data were from trials using the three times daily formulations. Overall, there were 44 deaths in patients treated with amoxicillin/clavulanate, 21 in patients with respiratory tract infection, 14 in patients with urinary tract infections and nine in patients with general/gastrointestinal infection. None of these deaths was considered by the investigators to be related to amoxicillin/clavulanate treatment. The majority of patients in these trials experienced no adverse events. Of the 13% of patients who reported an adverse event, 'gastrointestinal events' was the most common (8.4%), with 'body as a whole' (1.1%) and 'skin and appendages' (1.4%) being the only other adverse events experienced by more than 1% of patients. The incidence of upper gastrointestinal adverse events was 2.5%, with nausea the most common (1.4%). For lower gastrointestinal adverse events (3.7%), diarrhoea was the most common (3.4%). In 89 comparative trials, withdrawals due to any reason, including adverse events, were a median of 10% for amoxicillin/clavulanate versus 9% for comparators. Outside of this study, pseudomembranous colitis due to *Clostridium difficile* overgrowth has been reported with amoxicillin/clavulanate, as for other antimicrobials, and is a rare adverse event that can range from mild to life threatening in severity (prescribing information, GlaxoSmithKline). Other adverse events include cholestatic jaundice, changes in liver function tests and hypersensitivity reactions (pre-

scribing information, GlaxoSmithKline). Patients with known penicillin hypersensitivity should not be given amoxicillin, and amoxicillin/clavulanate should be used with caution in patients with evidence of hepatic dysfunction and amoxicillin/clavulanate is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with treatment with amoxicillin/clavulanate (prescribing information, GlaxoSmithKline).

More recently, a comparison of studies including 1191 adults with bronchitis, pneumonia or complicated urinary tract infection found no significant difference in the percentage of adverse events in patients receiving amoxicillin/clavulanate 875/125 mg twice daily versus 500/125 mg three times daily (prescribing information, GlaxoSmithKline). However, in a comparative study, patients receiving the 875/125 mg twice daily formulation reported less 'moderate to severe' diarrhoea (2.9%) versus those receiving 500/125 mg three times daily (4.9%) ($P = 0.28$).[32]

An early analysis of the pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg twice daily formulation found no differences in the frequency or nature of adverse events versus other amoxicillin/clavulanate formulations.[94] Although the amoxicillin dose of the 2000/125 mg formulation is increased versus conventional formulations, a component of this is released over a sustained period (875 mg). Thus, the peak serum concentration for the 2000/125 mg formulation (~16 mg/L) is similar to that of the 875/125 mg twice daily formulation (~11 mg/L) (Figure 1).[33,112] Without the sustained release component, a 2000/125 mg all immediate release formulation would achieve peak serum concentrations in the region of 22 mg/L (Figure 1).[33,94] The pharmacokinetics of the clavulanate component of the pharmacokinetically enhanced 2000/125 mg formulation remain unchanged compared with the 875/125 twice daily formulation. As the incidence of gastrointestinal adverse events is thought to be primarily related to clavulanate, no differences might be expected in gastrointestinal events between the 2000/125 mg dose and the 875/125 mg dose, both given twice daily.[113]

Two studies have been published comparing safety data for the pharmacokinetically enhanced 2000/125 mg formulation against the conventional 875/125 twice daily formulation.[82,95] No differences were found between the two formulations in the frequency or nature of adverse events in either of these studies. In patients with AECB, adverse events related to study medication were 21.9% (97/443) for the 2000/125 mg formulation versus 20.7% (93/450) for the 875/125 mg formulation (data on file, GlaxoSmithKline).[82] The most common adverse event was diarrhoea, experienced by 14.7% of patients in the 2000/125 mg group and 12.9% in the 875/125 mg group, but led to withdrawal in only 1.0% and 1.1% of patients, respectively. Withdrawals due to any adverse event were 2.3% for the 2000/125 mg group and 4.0% for the 875/125 mg group.

Similarly, in a study in CAP, 18.9% (61/322) of patients in the 2000/125 mg amoxicillin/clavulanate group experienced an adverse event thought to be related to study medication compared with 18.3% in the 875/125 mg group (data on file, GlaxoSmithKline).[95] Diarrhoea was the most common adverse event in both groups, experienced by 11.2% of patients in the 2000/125 mg group versus 9.3% in the 875/125 mg group, resulting in patient withdrawal in 0.3% of patients in both groups. Withdrawals due to any adverse event were also similar between the two groups: 2.2% for the 2000/125 mg formulation versus 3.9% for the 875/125 mg formulation.

In these two studies, the majority of diarrhoea was of mild-to-moderate intensity, with 2.9% and 2.2% of patients receiving the 2000/125 mg formulation and 3.6% and 3.9% receiving the 875/125 mg formulation requiring corrective treatment in the AECB study and CAP study, respectively (data on file, GlaxoSmithKline).[82,95]

The paediatric amoxicillin/clavulanate formulations are also generally well tolerated.[114] As with the adult formulations, the majority of adverse events are gastrointestinal disturbances and are mild and transient.[114] No serious adverse events were reported in a post-marketing surveillance study of 3048 children (≤14 years) receiving three times daily formulations of 300 to 450 mg/day.[115] There were 161 adverse events reported from 118 patients (3.9%) and, of these, 34 were thought to be related to study medication. Unfortunately, in this study the type of adverse event was not recorded.

Three AOM studies indicate that the incidence of diarrhoea may be lower for twice daily compared with three times daily amoxicillin/clavulanate regimens.[35,36,116] A comparison of amoxicillin/clavulanate 70/10 mg/kg/day in two divided doses ($n = 231$) versus 60/15 mg/kg/day in three divided doses ($n = 232$) reported diarrhoea rates of 6.7% and 10.7%, respectively.[35] Similarly, a study evaluating the more commonly used formulations, 45/6.4 mg/kg/day in two divided doses ($n = 209$) versus 40/10 mg/kg/day in three divided doses ($n = 206$) reported diarrhoea rates of 7.2% and 10.7%, respectively.[116] Although the difference in diarrhoea rates for these two studies did not reach statistical significance, they support the findings of a study that did show a significant difference in diarrhoea rates ($P = 0.0001$) with 8.7% of patients in the 45/6.4 mg/kg/day in two divided doses group ($n = 293$) versus 26.7% in the 40/10 mg/kg/day in three divided doses group ($n = 288$) experiencing this adverse event.[36]

A comparative study of the safety and tolerability of the high-dose paediatric amoxicillin/clavulanate 90/6.4 mg/kg/day formulation versus the conventional 45/6.4 mg/kg/day formulation found no significant differences in the nature or frequency of the adverse events between the two groups.[96] Adverse events (due to any cause) were reported for 50.2% (101/201) of patients in the amoxicillin/clavulanate 90/6.4 mg/kg/day group versus 47.3% (98/207) for the 45/6.4 mg/kg/day group. Although the new high-dose 90/6.4 mg/kg/day paediatric amoxicillin/clavulanate formulation contains double the amount of amoxicillin compared with the standard 45/6.4 mg/kg/day formulation, the amount of clavulanate remains the same. The incidence of protocol-defined diarrhoea was 11.0% in the 90/6.4 mg/kg/day group versus 8.8% in the 45/6.4 mg/kg/day group (95% confidence interval –3.8% to 8.3%).[96] There were also no differences in mean or maximum bowel movement frequency between the two groups.[96]

Conclusions

Whereas the development and spread of antimicrobial resistance in the major respiratory tract pathogens has compromised the efficacy of some commonly used antimicrobials, particularly those with suboptimal PK/PD parameters,[59,60,70,117] amoxicillin/clavulanate efficacy has remained robust in over 20 years of clinical use. Optimizing PK/PD to maximize bacterial eradication not only assures the highest probability of clinical cure, but may also reduce the development and spread of resistance.[50,51,103] For amoxicillin/clavulanate (and other β-lactams), $T > \text{MIC}$ is the critical PK/PD parameter predicting bacteriological eradication.[55,56,60] Amoxicillin/clavulanate has a favourable PK/PD profile that ensures the preservation of bacteriological efficacy against β-lactamase-producing *H. influenzae* and *M. catarrhalis*, as well as many clinical strains of *S. pneumoniae* with reduced penicillin susceptibility.[51,77,78,118] Enhancement of this PK/PD profile by increasing the amoxicillin dose (amoxicillin/

Table 3. Examples of treatment guideline recommendations for the use of amoxicillin/clavulanate in respiratory tract infections and AOM

Indication	Guidelines	Recommendations
ABS	Sinus and Allergy Health Partnership[24]	Amoxicillin/clavulanate as a first-line empirical therapy for both mild and moderate ABS
AECB	WHO Model Prescribing Information[119]	Amoxicillin/clavulanate as a treatment choice
CAP	American Thoracic Society[22]	A combination of amoxicillin/clavulanate plus a macrolide for adult outpatient therapy where the patient has additional risk factors, such as cardiopulmonary disease or the possible presence of drug-resistant *S. pneumoniae* or anaerobes
CAP	British Thoracic Society[120]	Oral amoxicillin for empirical therapy in the community
CAP	Spanish Society for Pulmonology and Thoracic Medicine[121]	Amoxicillin/clavulanate for non-severe CAP with a risk of resistant aetiology and in severe CAP with or without a risk of resistant pathogens
CAP	The French Infectious Disease Society (SPILF)[122]	Amoxicillin for a patient ≥40 years with no comorbidity; amoxicillin/clavulanate as a choice for older patients with comorbidity and for patients requiring hospitalization
AOM	US Centers for Disease Control[23]	Efficacy against *S. pneumoniae* is the most important factor in the empirical treatment of this disease; amoxicillin is the treatment of choice as it has a good pharmacodynamic profile against drug-resistant *S. pneumoniae*, but a combination of amoxicillin and clavulanate is also recommended as it extends the antimicrobial coverage to β-lactamase-positive strains of *H. influenzae* and *M. catarrhalis*
Otitis media	WHO Model Prescribing Information[119]	Amoxicillin/clavulanate for treatment of otitis media and as the preferred choice in regions where β-lactamase-producing strains of *H. influenzae* are common; high-dose amoxicillin/clavulanate is a treatment of choice where the prevalence of penicillin-resistant *S. pneumoniae* is increasing

clavulanate 90/6.4 mg/kg/day) or adding an extended-release component (amoxicillin/clavulanate 2000/125 mg twice daily) further extends antibacterial coverage to include most penicillin-resistant strains, including those with elevated amoxicillin MICs (up to 4 mg/L).[33,37,60,61,65,67,82,83,90,95,114]

As most respiratory tract infections are treated empirically, when choosing an antimicrobial it is important that all the major pathogens are considered, including the possibility of resistant strains. Recommendations for antimicrobial therapy in respiratory tract infection should be based on the principle of targeting bacterial eradication[50,51] and the use of PK/PD predictors of maximal bacterial eradication, and should reflect local resistance patterns.[51] Although, guidelines for the treatment of respiratory tract infection vary throughout the world, amoxicillin and amoxicillin/clavulanate are consistently included in recommendations (Table 3).[22–24,119–122] This reflects the high clinical and bacteriological efficacy of these agents against *S. pneumoniae* and of amoxicillin/clavulanate against β-lactamase-producing *H. influenzae* and *M. catarrhalis*.[27–32,34–36] In addition, amoxicillin/clavulanate has a well known, established safety profile,[93] and extensive clinical use in over 819 million patients worldwide. Reassuringly, the safety profiles of both amoxicillin/clavulanate 90/6.4 mg/kg/day and amoxicillin/clavulanate 2000/125 mg twice daily are not significantly different from those of conventional formulations.[82,93–96,114]

The addition of high-dose formulations, such as amoxicillin/clavulanate 90/6.4 mg/kg/day, as well as the development of amoxicillin/clavulanate 2000/125 mg twice daily, provides additional assurance in treating bacterial infections that may involve pathogens with reduced susceptibility to other antimicrobials and may also minimize the selection and emergence of future resistant strains. The innovative combination of amoxicillin and clavulanate, originally and newly designed to provide activity against resistant bacteria, continues to be a valuable clinical tool for the treatment of respiratory tract infection both now and in the future.

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