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Clinical Role of β-Lactam/β-Lactamase Inhibitor Combinations

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Abstract

The use of β-lactamase inhibitors in combination with β-lactam antibiotics is currently the most successful strategy to combat a specific resistance mechanism. Their broad spectrum of activity originates from the ability of respective inhibitors to inactivate a wide range of β-lactamases produced by Gram-positive, Gram-negative, anaerobic and even acid-fast pathogens. Clinical experience confirms their effectiveness in the empirical treatment of respiratory, intra-abdominal, and skin and soft tissue infections. There is evidence to suggest that they are efficacious in treating patients with neutropenic fever and nosocomial infections, especially in combination with other agents. β-Lactam/β-lactamase inhibitor combinations are particularly useful against mixed infections. Their role in treating various multi-resistant pathogens such as *Acinetobacter* species and *Stenotrophomonas maltophilia* are gaining importance. Although, generally, they do not constitute reliable therapy against extended-spectrum β-lactamase producers, their substitution in place of cephalosporins appears to reduce emergence of

the latter pathogens. Similarly, their use may also curtail the emergence of other resistant pathogens such as *Clostridium difficile* and vancomycin-resistant enterococci. β-Lactam/β-lactamase inhibitor combinations are generally well tolerated and their oral forms provide effective outpatient therapy against many commonly encountered infections. In certain scenarios, they could even be more cost-effective than conventional combination therapies. With the accumulation of so much clinical experience, their role in the management of infections is now becoming more clearly defined.

Growing bacterial resistance is a global emergency such that direct targeting and reversal of the underlying resistant mechanisms has become imperative.[1] Currently the use of β-lactamase inhibitors (clavulanic acid [clavulanate], sulbactam, tazobactam) is the most successful strategy to restore the efficacy of β-lactam antibiotics. This article reviews the pharmacology, clinical experience, implications and limitations pertaining to these drugs with a view to defining their current role in clinical practice.

1. β-Lactamases

β-Lactamases hydrolyse the amide bond in the β-lactam ring and prevent the active drug from reaching target penicillin-binding proteins (PBPs). The latter are transpeptidases, carboxypeptidases and endopeptidases, the enzymes responsible for cross-linkages between peptidoglycans within bacterial cell walls. Over 340 β-lactamases have been described and are classified according to their substrate profile (penicillinases, cephalosporinases, carbapenemases) and susceptibility to inhibition by clavulanate (e.g. Bush functional groups 1-4); or molecular weight and genetic determinants (Ambler classes A-D).[2] The majority of Gram-negative bacteria, staphylococci, anaerobes and even mycobacteria[3] produce β-lactamases (table I); while streptococci, pneumococci and most enterococci do not. As they could be encoded chromosomally or by plasmids, wide distribution of resistance ensues. The most common β-lactamases produced by Enterobacteriaceae, such as TEM-1/-2 and SHV-1, and staphylococcal penicillinases (all belonging to Bush group 2/Ambler class A), are generally plasmid-mediated. These enzymes can be effectively inhibited by β-lactamase inhibitors unless the latter are overwhelmed by β-lactamase hyperproduction.[4,5] β-lactamases produced by anaerobes, particularly from *Bacteroides* and *Fusobacterium* species are also susceptible.[6,7]

Higher generation cephalosporins initially designed to escape from enzymatic degradation are now losing merit, as single step mutations from the basic enzymes referred to as the TEM/SHV series create extended spectrum β-lactamases (ESBLs) [e.g. TEM 3-26, SHV 2-6]. Thus, in addition to penicillins, they are capable of inactivating antibiotics, such as ceftazidime, cefotaxime, ceftriaxone and aztreonam (all possessing aminothiazole-oxime groups), to varying extents.[2] By and large, ESBLs are readily inhibited by available inhibitors *in vitro*. However, at least nine types of 'clavulanate resistant TEM' mutants (also known as inhibitor-resistant TEMs or IRTs) have been recognised.[5] With few exceptions, chromosomally encoded broad-spectrum cephalosporinases (Bush 1/Ambler class C) are intrinsically inhibitor non-susceptible (table I). Besides being inducible by various β-lactams, including certain cephalosporins, imipenem and even clavulanate, derepressed/mutated *ampC* gene complexes lead to constitutive hyper-production of the respective β-lactamase.[5] Transposition of these resistant genes onto plasmids may facilitate their wide

Table I. Characteristics of common β-lactamases and the pathogens that typically produce them[1,2,6,8][a]

Inhibitor susceptible	Inhibitor non-susceptible
Characteristics	
Constitutive production	Inducible or constitutive production
Plasmid mediated	Chromosome encoded
Bush group 2 or Ambler class A penicillinases	Bush group 1 or Ambler class C cephalosporinases
Examples[b]	
Staphylococcus aureus (>90)	*Enterobacter* spp., *Citrobacter* spp.
Haemophilus influenzae e.g. TEM-1 (16–36)	*Serratia* spp., *Providencia* spp.
Escherichia coli,[cd]*Klebsiella* spp.[ed] and *Proteus* spp. e.g. TEM-1/-2, SHV-1 (30–60)	*Morganella* spp.[f]
Moraxella catarrhalis[e] e.g. BRO-1/-2 (>90)	*Acinetobacter* spp.
Bacteroides fragilis[e] (>90)	*Pseudomonas* spp.[ed] (20–50)

a *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa* and *Bacteroides fragilis* can also mediate inhibitor non-susceptible Bush group 3 or Ambler class B metalloenzymes/carbapenemases.

b Percentage of clinical isolates (worldwide) that produce the respective enzymes are shown in parenthesis.

c Virtually all members of the Enterobacteriaceae (except *Klebsiella* and *Salmonella* spp.) can produce Ambler class C cephalosporinases to various extents.

d Common ESBL producers.

e Also produce inhibitor-susceptible, chromosomally encoded enzymes.

f Some of their β-lactamases are susceptible to tazobactam inhibition.

ESBL = extended spectrum β-lactamases.

spread dissemination.[5] β-lactamase inhibitors may also be considered ineffective in situations where ESBL production co-exists with Ambler class C β-lactamase hyperproduction, or when other resistant mechanisms predominate (PBP alterations, drug efflux pumps, or change of membrane permeability due to loss of porins).[2]

2. Pharmacology

2.1 Pharmacodynamics

Clavulanate, sulbactam and tazobactam are the only β-lactamase inhibitors currently available for clinical use. Clavulanate is produced naturally by *Streptomyces clavulgerus*, whereas sulbactam and tazobactam are synthetic penicillanic acid sulfones structurally related to penicillin.[4] They irreversibly inhibit β-lactamases via acyl-enzyme complex formation, which allows the intact accompanying penicillin or cephalosporin to exhibit time-dependent bacterial killing (usually through binding to PBP-1 and -3). Only sulbactam possesses intrinsic antimicrobial activity, exerted through PBP-2 targets. The latter property is exploited with success against infections due to *Acinetobacter* species, *Bacteroides fragilis* and glycopeptide intermediate-resistant *Staphylococcus aureus* (GISA), and also provides synergism with β-lactams in other scenarios.[7-9]

β-lactamase inhibitors lower the corresponding minimum inhibitory concentrations (MIC) against individual bacterial isolates. For instance, against β-lactamase producing *Haemophilus influenzae*, addition of sulbactam or clavulanate lowered the MIC of cefoperazone or amoxicillin from 0.25–0.5 to 0.06 mg/L and >64 to 1.0 mg/L, respectively.[7,10] The possibility that inoculum effect (usually inferred whenever MICs increase in the presence of higher bacterial counts) may be partially redressed by the addition of inhibitors remains controversial.[11]

While all three inhibitors in conventional doses are regarded as clinically equivalent at counteracting common (TEM-1/SHV-1) β-lactamases, considerable differences exist towards various ESBLs, class C enzymes and those released by anaer-

Table II. Currently used β-lactam/β-lactamase inhibitor combinations[4,20]a

Inhibitor	β-lactam	Approved/trade name of combination	Route
Clavulanate	Amoxicillin	Co-amoxiclav, Augmentin®b	PO, IV
Clavulanate	Ticarcillin	Timentin®	IV
Sulbactam	Ampicillin	Sultamicillin,c Unasyn®	PO,c IV
Sulbactam	Cefoperazone	Sulperazon®c	IV
Tazobactam	Piperacillin	Tazocin®, Zosyn®	IV

a β-lactam/inhibitor ratios in each formulation of piperacillin/tazobactam, cefoperazone/sulbactam, ticarcillin/clavulanate and oral ampicillin/sulbactam (sultamicillin) and amoxicillin/clavulanate (co-amoxiclav) are typically 8 : 1, 1–2 : 1, 15–30 : 1, 1.5 : 1 and 2–4 : 1, respectively. Corresponding ratios for parenteral ampicillin/sulbactam and co-amoxiclav are 2 : 1 and 5 : 1. Note that IV co-amoxiclav contains a smaller proportion of clavulanate than oral formulations, presumably because it is not subject to first pass effect by the parenteral route and, therefore, attains higher systemic bioavailability. Compared with corresponding treatment with the β-lactam alone, drug costs (refers to Hong Kong costs for which corresponding treatment with β-lactam alone was available) of the β-lactam/inhibitor combinations ranged from about 13–19-fold as much for oral formulations and 2–12-fold as much by the parenteral route.

b Use of tradenames is for product identification only and does not imply endorsement.

c Orally administered combination prodrug, not available for commercial use in US.

IV = intravenous; **PO** = oral.

obes.[4,7,12] In this context, tazobactam provides the broadest spectrum of inhibition. Investigation of carbapenem derivatives that inhibit carbapenemase and certain class C β-lactamases, are now underway.[13] Clavulanate, but not sulbactam or tazobactam, induces class C β-lactamases *in vitro*, raising concerns that during treatment of *Pseudomonas aeruginosa* infections with ticarcillin/clavulanate, the effect of ticarcillin may become compromised.[14] In this context, piperacillin or cefoperazone have less induction potential than carbenicillin, cefazolin, cefoxitin, ceftazidime, ceftriaxone and cefotaxime, and are therefore preferred in combination with inhibitors.[14]

2.2 Pharmacokinetics

The perceived need for 'drug partners' to have similar elimination rates in order to maintain a fixed β-lactam/inhibitor concentration ratio in target tissues (even in the presence of disease states, e.g. renal failure), also restricts the scope for such combinations (table II).[15] The addition of inhibitor does not ameliorate the need for frequent administration; β-lactam serum concentration above MIC for >40% of the time is necessary to optimise bacterial killing and reduce emergence of resistant strains.[16] The elimination half-lives of inhibitors range from 0.5–1.0 hours, and the usual administration interval of drug combinations is 6–8 hours. Exceptionally, intravenous cefoperazone/sulbactam and oral ampicillin/sulbactam may be given 12 hourly because of their longer half-lives (up to 2.6 hours for cefoperazone) when used in combination.[17-19] For serious infections, cefoperazone/sulbactam should be given as 2g doses, although for mild infections involving organisms with a relatively low MIC, a lower dose may suffice. This is because peak post-infusion concentrations following cefoperazone 2g are sufficiently high (exceed 140 mg/L).[18,19]

Whereas tazobactam, sulbactam and most accompanying β-lactams are excreted via the renal route, clavulanate undergoes extensive metabolism into inactive metabolites. In patients with renal failure for whom the dosage interval of these combinations is usually increased (guided by creatinine clearance), the resultant deficiency of clavulanate relative to ticarcillin is believed to reduce bacterial killing.[21] Excretion of cefoperazone in bile, offers a theoretical advantage for treating biliary tract infections with cefoperazone/sulbactam.[17,22] Generally β-lactamase inhibitors distribute well into various body fluids and tissues (e.g. middle ear, lung, biliary

tract, peritoneum), with sulbactam having the largest volume of distribution.[15] In contrast to higher generation cephalosporins, data regarding cerebrospinal fluid penetration of these combination products is meagre. Thus, to date they are not recommended for treating central nervous system infections.

Orally, sulbactam together with ampicillin are not used as a mixture but as the combined double-ester prodrug sultamicillin. The latter is metabolically cleaved into its two constituents after being absorbed. In contrast to ampicillin alone, like amoxicillin/clavulanate, the ampicillin/sulbactam prodrug is much more readily and consistently absorbed from the gut. Thus orally, amoxicillin/clavulanate and ampicillin/sulbactam both attain high systemic bioavailability (about 90 and 80%, respectively), and depending on the formulation, twice or three time daily dose administration generally suffices.[23,24] Since it is more convenient and cost-effective, the oral route is therefore recommended whenever feasible and appropriate.[25]

2.3 Adverse Effects

β-lactam/β-lactamase inhibitor combinations are generally well tolerated. Compared with taking the β-lactam component alone, the incidence of adverse effects, namely, diarrhoea, abnormal liver function tests (typically mild and reversible) and skin rashes, have been reported to be slightly higher.[4,20,23,24] *Clostridium difficile*-associated diarrhoea occurs less frequently with piperacillin/tazobactam than cephalosporins, which is possibly related to the activity against anaerobes of the former.[26] Ampicillin/sulbactam or amoxicillin/clavulanate are more controversial in this respect.[23,24] In contrast, oral amoxicillin/clavulanate has been associated with non-infective, clavulanate dose-dependent diarrhoea in up to 10% of treated persons and possibly more frequently in children.[23] Clavulanate co-administered with allopurinol increases the risk of skin rash.[20] Very rarely, clavulanate also induces reversible, non-fatal cholestatic hepatitis; advanced age, male gender and prolonged therapy being independent risk factors.[27] Cefoperazone-related coagulopathy and ticarcillin- or piperacillin-related salt overload, are other special considerations relevant to the use of these drug combinations.[4]

3. Role of β-Lactam/β-Lactamase Inhibitor Combinations in Various Clinical Settings

The overall antibacterial spectrum of these drug combinations depends on the intrinsic activity of the β-lactam (PBP binding, drug permeation, etc.) as well as the characteristics of the individual inhibitor towards different β-lactamases. As noted (table I), methicillin-sensitive *S. aureus* (MSSA), *H. influenzae*, *Moraxella catarrhalis*, *Bacteroides* spp. and many Enterobacteriaceae species, such as *Escherichia coli*, *Klebsiella* and *Proteus* spp. are generally susceptible. Streptococci, pneumococci, enterococci and even *Pseudomonas* spp. are susceptible depending on the accompanying β-lactam. Combinations containing piperacillin or cefoperazone offer the broadest antibacterial spectrum. When used alone, even potent cephalosporins such as ceftazidime will not provide satisfactory activity against Gram-positive pathogens or anaerobes.

Accumulating experience with β-lactam/β-lactamase inhibitor combinations has resulted in a better appreciation of their role in clinical practice. Importantly, they are indicated for the empirical treatment of a variety of infections (table III), particularly against mixed infections involving anaerobes and against certain multi-resistant pathogens responsible for nosocomial infections.[28,29] When compared with more conventional regimens, β-lactam/β-lactamase inhibitor combinations are relatively well tolerated and are at least as efficacious if not superior (table IV). The available oral formulations also provide convenient outpatient or step-down therapy against susceptible pathogens.

Table III. Summary of clinical indications for β-lactam/β-lactamase inhibitor combinations[4,7,17,23,24,30-40]

Type of infection	Amoxicillin/ clavulanate[4,23]	Ampicillin/ sulbactam[4,24]	Ticarcillin/ clavulanate[4,17]	Cefoperazone/ sulbactam[7,17]	Piperacillin/ tazobactam[4,17]
Upper respiratory	++	+			
Lower respiratory	++	+	++	+	++
Urinary	++	+	++	+	+
Intra-abdominal		++	++	+	++
Gynecologic		++	++	+	++
Skin and soft tissue	++	++	++	+	++
Neutropenic fever	+			+	+
Surgical prophylaxis	+	+		+	

++ = US FDA labelled uses with supporting published data; **+** = supporting published data available.

3.1 Respiratory Tract Infections

Common bacterial pathogens involved in sinusitis and otitis media are *H. influenzae*, *M. catarrhalis* and *Streptococcus pneumoniae*. Oral amoxicillin/clavulanate or ampicillin/sulbactam provide effective, convenient and relatively well tolerated empirical treatment for this purpose in both adult and paediatric general practice.[23,24] Whereas acute bacterial pharyngitis is mostly due to non-β-lactamase producing group A streptococci, amoxicillin/clavulanate therapy has been recommended for recurrent culture-positive patients in whom it achieves higher rates of pathogen eradication; killing of co-pathogenic anaerobes in the tonsillar area being the putative explanation.[41] Similarly, ampicillin/sulbactam and piperacillin/tazobactam are suitable against oral cavity, and head and neck infections in otherwise healthy and immunocompromised patients, respectively.[42,43] Apparently, amoxicillin/clavulanate reduces penicillin-resistant *S. pneumoniae* (PRSP) nasal carriage in the community more effectively than oral cephalosporins, macrolides or co-trimox-

Table IV. Summary of selected clinical trials comparing β-lactam/β-lactamase inhibitor combinations with other antibacterial regimens for different clinical indications

Type of infection	Regimens compared	Clinical/microbiological response rates (%)
Community-acquired	Amoxicillin/clavulanate (IV)[30] vs clarithromycin	84 vs 86
pneumonia	Amoxicillin/clavulanate (PO)[30] vs levofloxacin	86 vs 84
Hospital-acquired	Piperacillin/tazobactam + amikacin[31] vs ceftazidime + amikacin	51 vs 36
pneumonia	Piperacillin/tazobactam[32] vs imipenem/cilastatin	83 vs 71
Intra-abdominal infection	Piperacillin/tazobactam[32] vs imipenem/cilastatin	95 vs 93
	Piperacillin/tazobactam[33] vs imipenem/cilastatin	91 vs 69[a]
	Piperacillin/tazobactam[4] vs clindamycin + gentamicin	88 vs 77
	Cefoperazone/sulbactam[34] vs imipenem/cilastatin	56 vs 68
	Ampicillin/sulbactam[4] vs clindamycin + gentamicin	87 vs 97
Skin and soft tissue	Ampicillin/sulbactam[39] vs imipenem/cilastatin	81 vs 85
infection	Ampicillin/sulbactam[40] vs cefoxitin	90 vs 94
Neutropenic fever	Piperacillin/tazobactam + amikacin[35] vs ceftazidime + amikacin	61 vs 54[a]
	Piperacillin/tazobactam + amikacin[36] vs cefepime + amikacin	51 vs 49
	Cefoperazone/sulbactam[37] vs imipenem/cilastatin	88 vs 81
	Amoxicillin/clavulanate[38] vs ceftazidime, plus ciprofloxacin (PO)	71 vs 67
	Amoxicillin/clavulanate[38] vs ceftriaxone + amikacin, plus ciprofloxacin (PO)	86 vs 84

a Statistically significant difference.

IV = intravenous; **PO** = oral.

azole (trimethoprim/sulfamethoxazole).[44] The slightly lower MIC of amoxicillin *in vitro* compared with penicillin is a possible explanation. Despite a net reduction in PRSP nasal carriage under these circumstances, ironically the proportion of *S. pneumoniae* that are penicillin-resistant increases, presumably because amoxicillin/clavulanate has more effect on penicillin-sensitive than penicillin-resistant pneumococci. In view of these observations, the impact of amoxicillin/clavulanate on the PRSP pandemic warrants further study.[45]

The role of β-lactam/β-lactamase inhibitor combinations in treating community acquired pneumonia (CAP) has been discussed in several authoritative published guidelines.[30,46] Depending on local prevalence, empirical antibacterial therapy should be directed against *S. pneumoniae* (including PRSP), *H. influenzae*, *M. catarrhalis*, MSSA, 'atypical pathogens' (*Mycoplasma*, *Chlamydia* and *Legionella* spp.) and, under appropriate clinical settings, Gram-negative bacilli and anaerobes. According to a worldwide surveillance programme, up to 99% of *H. influenzae* and *M. catarrhalis* clinical isolates are sensitive to amoxicillin/clavulanate, which is comparable or superior to most oral cephalosporins.[8] In the same study, less than 3% of *S. pneumoniae* had *in vitro* resistance to amoxicillin/clavulanate; despite an overall resistance of 10–18% to penicillin and 9–39% to oral cephalosporins or macrolides.

PRSP mediate resistance via mutations of PBP. According to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines, an MIC breakpoint of 0.1–1.0 mg/L could be used to define PRSP with intermediate penicillin resistance. However, the corresponding MIC breakpoints are now regarded as overestimates, as they were originally derived for the treatment of meningitis not pneumonia. It is now accepted that so long as the serum concentration exceeds the MIC during 40–50% of the dose administration interval, an isolate may be regarded as susceptible to penicillins.[47] In general, for isolates with an amoxicillin MIC ≤2 mg/L such drug concentrations can be readily achieved even by the oral route (figure 1).[48] Theoretically, a single 875mg oral dose of amoxicillin provides about 42% coverage time above MIC against a PRSP isolate that has an MIC of 2 mg/L during a 12-hourly dose administration interval. Similarly, amoxicillin 500mg administered every 8 hours provides a corresponding coverage time of about 65% against a PRSP isolate that has an MIC of 1 mg/L.[49]

Few other oral β-lactams show such favourable pharmacokinetic and pharmacodynamic proper-

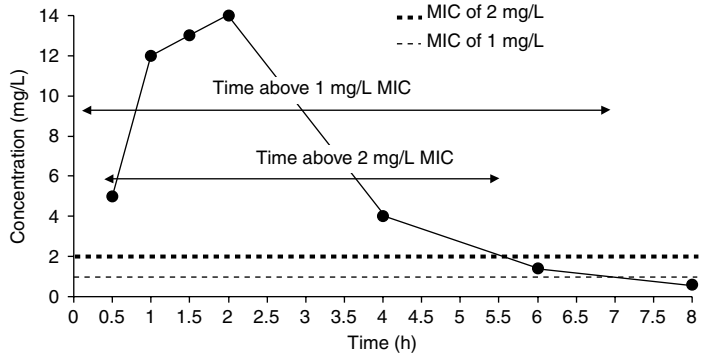

Fig. 1. Serum amoxicillin concentrations after a single oral dose of amoxicillin 875mg/clavulanic acid 125mg. The amoxicillin concentration exceeds its minimum inhibitory concentration (MIC) of 2 mg/L and 1 mg/L against *Streptococcus pneumoniae* isolates with differing degrees intermediate grade penicillin resistance for approximately 42% (5/12 hours) and 58% (7/12 hours) of each 12 hour dosage interval, respectively. Reprinted from Thorburn et al.,[48] with permission from the American Society for Microbiology.

ties.[49] Moreover against PRSP, amoxicillin shows greatest *in vitro* activity followed by ampicillin, penicillin, piperacillin and ticarcillin in that order.[42,46] Among cephalosporins, cefotaxime or ceftriaxone constitute more reliable therapy for PRSP because they have lower MICs against *S. pneumoniae* than cefuroxime or ceftazidime.[30,46] Although requiring further evaluation, oral amoxicillin/clavulanate is seemingly an attractive treatment option for patients with mild CAP or as step-down/outpatient therapy, especially in regions where intermediate penicillin-resistant and/or high grade (via target modification) macrolide-resistant *S. pneumoniae* are prevalent. Under these circumstances, empirical macrolide monotherapy may become unreliable. Since β-lactam antibiotics like amoxicillin/clavulanate do not possess activity against *Mycoplasma*, *Chlamydia* or *Legionella* species, dual therapy with a macrolide is usually recommended.

For the more seriously ill patients with CAP in general medical wards and intensive care unit (ICU) settings, amoxicillin/clavulanate (if available), ampicillin/sulbactam or piperacillin/tazobactam should be used intravenously initially, so as to attain high drug concentrations quickly. In this context, concomitant administration of a macrolide or fluoroquinolone is again preferable.[30,46] However, in a retrospective analysis[50] of CAP in elderly patients, the use of β-lactam/inhibitor combinations together with a macrolide was associated with a higher 30-day mortality than other regimens. Ironically, the latter regimens included β-lactam/inhibitor combinations used alone. The explanation postulated was that a macrolide was added to an already failing therapy. Notably, ticarcillin/clavulanate was associated with a higher mortality rate than ampicillin/sulbactam or piperacillin/tazobactam. This observation appears compatible with the intrinsic differences in activity of the respective β-lactams against *S. pneumoniae*. Further prospective studies are clearly warranted to resolve this issue.

Whereas β-lactam antibiotics are generally still effective against *S. pneumoniae*, increasingly encountered resistance to fluoroquinolones, especially among patients with chronic obstructive pulmonary disease, has fuelled moves to relegate fluoroquinolone monotherapy from among the first-line drugs to treat such respiratory infections.[51] β-lactam/inhibitor combinations are also useful in treating aspiration pneumonia because of their activity against anaerobes, such activity is not possessed by many cephalosporins.[17,30,46] Cost-effectiveness issues pertaining to the use of these drugs in CAP need to be addressed further, as generally they are more expensive than their β-lactam components alone.[52,53]

For nosocomial and ventilator-associated pneumonia, piperacillin/tazobactam or cefoperazone/sulbactam provide suitable empirical therapy, as MSSA, Enterobacteriaceae and *P. aeruginosa* are all generally susceptible.[7,8,31] Clinical success rates approaching 80% have been demonstrated for piperacillin/tazobactam, which is comparable to rates achieved with ceftazidime plus amikacin or monotherapy with imipenem/cilastatin.[4,31,32] Nevertheless, in patients with serious culture-documented pseudomonal pneumonia, it is not unusual to employ a combination regimen that also includes ciprofloxacin or an aminoglycoside to facilitate possible synergism.[29,30,46] Ticarcillin/clavulanate is less reliable in this respect and this is possibly related to the intrinsically higher MIC of ticarcillin against *P. aeruginosa*.[14,17]

3.2 Urinary Tract Infections

In uncomplicated urinary infections, >80% of which are due to *E. coli*, at one time cure rates of 80–90% were reported after treatment with oral amoxicillin/clavulanate or ampicillin/sulbactam.[23,24] These success rates may no longer be attainable, because of the emergence of certain *E. coli* and *Proteus mirabilis* strains that encode for

inhibitor-resistant β-lactamases (IRT) or deploy alternative resistance mechanisms. Such resistance has been reported in up to 7–8% of urinary isolates.[2,5,54] Piperacillin/tazobactam tends not to select for these pathogens and remains effective even in complicated urinary tract infections,[55] consistent with the greater activity of tazobactam than clavulanate or sulbactam against IRT strains.[5] Despite the limitations of β-lactam/inhibitor combinations in treating systemic infections by ESBL producing pathogens, in exclusively lower urinary tract infections they may nevertheless overwhelm such pathogens by achieving very high urinary drug concentrations due to their renal elimination.[1,2,5,11,56]

3.3 Intra-Abdominal Infections

For the treatment of intra-abdominal infections, such as peritonitis, abscesses and biliary sepsis, empirical use of antibiotics is usually directed against aerobic Gram-negative bacilli and anaerobes, such as *B. fragilis*. β-Lactam/β-lactamase inhibitor combinations containing sulbactam and tazobactam are particularly useful because, besides activity against gram-negative bacilli, they have comparable efficacy to clindamycin, cefoxitin or metronidazole against anaerobes.[6] Standard regimens involving combinations consisting of one of the latter agents together with cephalosporins and aminoglycosides are complicated and adverse effects are frequent.[17] In comparison, use of piperacillin/tazobactam is relatively simple and avoids drug concentration monitoring. Moreover, as clinical response rates approach 90%, this β-lactam/inhibitor combination appears as efficacious and possibly more cost-effective than older regimens or imipenem/cilastatin monotherapy.[32,33,57] Cefoperazone/sulbactam also achieved similar results.[34] Similar evidence supports the use of sulbactam combinations for surgical chemoprophylaxis, especially in the course of elective colorectal surgery to prevent post-operative wound infections.[58] However, the increasing extent of *B. fragilis* resistance to sulbactam (up to 7%) deserves attention.[6,59] Notably, β-lactam/inhibitor combinations containing ampicillin, amoxicillin and piperacillin (but not ticarcillin or cefoperazone) enable treatment of infections involving enterococci, which possibly take on pathogenic significance in immunocompromised patients.[17]

3.4 Neutropenic Fever

Neutropenic fever is regarded as a medical emergency, mandating immediate, empirical intervention with broad-spectrum antibacterials, although the responsible pathogens are frequently difficult to identify. The widespread use of antibacterial prophylaxis against Gram-negative pathogens appears to have rendered such patients liable to Gram-positive bacterial infections, particularly those due to viridans streptococci and coagulase-negative staphylococci.[29,60] In this context, piperacillin/tazobactam plus amikacin was reported to yield superior clinical results to ceftazidime plus amikacin and a lower incidence of superinfections, and was as efficacious as cefepime plus amikacin.[4,35,36] In other comparisons, cefoperazone/sulbactam plus amikacin achieved similar efficacy to imipenem/cilastatin, whereas ticarcillin/clavulanate appeared less satisfactory.[17,37] While piperacillin/tazobactam plus amikacin has become an accepted regime for neutropenic fever, the use of piperacillin/tazobactam monotherapy without the addition of an aminoglycoside is more controversial.[61] In low-risk patients expected to have <10 days of neutropenia and no other co-morbidity, empirical therapy for fever with oral amoxicillin/clavulanate plus ciprofloxacin was evidently as effective and well tolerated as intravenous therapy with a third-generation cephalosporin ± amikacin.[38,61] Thus, β-lactam/β-lactamase inhibitor combinations hold out promise for preventing nosocomial infections possibly by virtue of outpatient therapy. Some authorities recommend amoxicillin/clavulanate as 'standby' therapy for fever in

asplenic patients since the latter is active against *S. pneumoniae*, *H. Influenzae* and meningococci; but this practice still requires verification.[62]

3.5 Skin and Soft Tissue Infections

While skin and soft tissue infections, such as cellulitis, are commonly caused by *S. aureus* or group A streptococci, deep/surgical wound infections or those in compromised hosts (e.g. diabetic/ischaemic foot infections, decubitus sores) are often polymicrobial and involve anaerobes and Gram-negative pathogens. Although amoxicillin/clavulanate or ampicillin/sulbactam (intravenously and even orally) are considered effective alternatives to treat superficial infections, in general they offer no additional advantage over cloxacillin or cefazolin and are more costly.[23,24] However, amoxicillin/clavulanate is considered a drug of choice in the empirical treatment of infections related to bites by cats and dogs, as it is active against incriminated pathogens such as *Pasteurella multocida*.[63]

β-Lactam/β-lactamase inhibitor combinations nevertheless provide the necessary broad-spectrum antimicrobial activity to overcome mixed infections.[64] Clinically, ampicillin/sulbactam is as efficacious but more cost-effective than imipenem/cilastatin in treating diabetic foot infections and comparable to cefoxitin in managing cellulitis in intravenous drug users.[39,40] Piperacillin/tazobactam has also been used successfully in more serious/complicated infections.[4,64] Whether substitution of cefazolin and cefoxitin by β-lactam/β-lactamase inhibitor combinations can reduce the selection pressure on *ampC* mutants and methicillin-resistant *S. aureus* (MRSA) is still to be resolved.[65] Clinical evidence also supports the use of such combinations in various gynaecological infections (e.g. pelvic inflammatory disease) but additional cover against *Chlamydia* spp. is advisable.[4,17]

3.6 Special Pathogens & Nosocomial Infections

MRSA manifests resistance by virtue of mutated PBPs with low β-lactam binding affinity, thus rendering it non-susceptible to β-lactam/inhibitor combinations. Occasionally, β-lactamase hyperproducing strains (also known as borderline oxacillin-resistant *S. aureus* or BORSA) may mimic MRSA phenotypically. Although appearing methicillin-resistant upon sensitivity testing, in experimental models they are susceptible to high doses of β-lactamase inhibitors and sometimes genetic testing is required to confirm their true identity.[66] According to a case report and experimental data, ampicillin/sulbactam plus arbekacin (a novel aminoglycoside) in conjunction with surgical debridement, may be effective in treating GISA, although the mechanisms involved are complex.[9,67]

Piperacillin/tazobactam, cefoperazone/sulbactam and, to a lesser extent, ticarcillin/clavulanate possess satisfactory activity against *Pseudomonas* species.[4,17,68] Nevertheless, against known infections with such difficult to treat pathogens, it is recommended that these β-lactam/β-lactamase inhibitor combinations be used with an aminoglycoside or fluoroquinolone in order to exploit possible synergy.[17] Notably, in addition to activity against plasmid-mediated pseudomonal β-lactamases, tazobactam is active against some of their chromosomally mediated enzymes. Overall, susceptibility of clinical isolates to piperacillin/tazobactam is >85%, which is somewhat superior to piperacillin alone.[8] Although appearing to be an attractive therapeutic option in the context of possible rapidly emerging imipenem or ciprofloxacin resistance, other factors such as loss of porins or the presence of efflux pumps may limit its efficacy and create multi-drug resistant strains.[2,8] Among β-lactams, ticarcillin/clavulanate has unique intrinsic activity against the carbapenemase producing, multi-drug resistant *Stenotrophomonas maltophilia*. Depending on the

results of sensitivity testing, it can therefore be used alone or synergistically with co-trimoxazole in more serious infections; overall >85% of isolates are susceptible.[8] Typically, the common nosocomial pathogen *Acinetobacter baumannii* is also multi-drug resistant, except to sulbactam, polymyxin and carbapenems. While the incidence of carbapenem-resistant strains is increasing, >90% of the strains retain *in vitro* susceptibility to ampicillin/sulbactam or cefoperazone/sulbactam.[8,69] Cefoperazone/sulbactam plus co-trimoxazole therapy has comparable clinical efficacy to the more traditional ceftazidime plus co-trimoxazole combination regimens against acute *Burkholderia pseudomallei* infection (melioidosis; prevalent in certain parts of south-east Asia), whereas oral amoxicillin/clavulanate is useful for suppressing relapses.[70,71]

Cutaneous infections due to *Nocardia brasiliensis* frequently involve β-lactamase production and can be effectively treated with amoxicillin/clavulanate.[43] The efficacy of β-lactam/inhibitor combinations against *Mycobacterium* species is also being recognised. Such optimism is based on *in vitro* data and studies in animal models involving successful treatment of infections with *Mycobacterium tuberculosis*, *M. leprae* and atypical mycobacterium species with ampicillin/sulbactam.[3] Further studies to explore the clinical relevance of β-lactam/inhibitor combinations in human mycobacterial infections are clearly warranted.

In many parts of the world, 5–25% of *E. coli*, and *Klebsiella* and *Pseudomonas* spp. isolates are now producing ESBLs, which is ascribed to selection pressure due to extensive use of late-generation cephalosporins.[2,8] ESBLs are susceptible to β-lactamase inhibitors; indeed β-lactam/clavulanate synergy is actually used for their detection.[5,72] For TEM-derived ESBLs, sulbactam appears to be a slightly more efficient inhibitor than tazobactam or clavulanate; whereas against SHV-derived ESBLs, clavulanate is slightly more effective.[12,73] Despite *in vitro* sensitivity to these antibiotics, clinical failure rates of >50% have been reported[74] as co-existing resistance mechanisms (e.g. TEM enzyme hyperproduction, concomitant AmpC expression or loss of porins) appear to be operating. Since ESBL producers carry resistance genes for other drug groups (e.g. aminoglycosides, fluoroquinolones) on the same plasmid, therapeutic options are rather limited.[1] Carbapenems constitute the only reliable therapy as they are stable in the presence of all serine based β-lactamases.[74] Strategies that can be deployed to prevent the dissemination of ESBL producing pathogens include stringent infection control measures and minimising selection pressure through curtailing the use of incriminated antibacterials.[56] Multiple studies have demonstrated that restricting third-generation cephalosporin use curtails the emergence of ESBL producers, mostly by means of substituting piperacillin/tazobactam.[75-78] The low propensity of piperacillin/tazobactam to select ESBL producing and *ampC* mutant pathogens is also evident from *in vitro* observations.[12,73,79,80] Although the activity of tazobactam against Ambler class C β-lactamases (particularly for certain pseudomonal enzymes) is reported to be superior to sulbactam and clavulanate, it does not constitute reliable therapy as >50–65% of such isolates are resistant,[81] and cefepime or carbapenems are clearly more reliable treatment options.[77]

Implementing policies similar to those described in the previous paragraph has also reduced the incidence of *C. difficile*-associated diarrhoea, rectal carriage of glycopeptide-resistant enterococci and even MRSA, which has far reaching and important implications.[26,65,82-84] Thus, in response to a rising incidence of infections due to certain resistant pathogens, strategic antibacterial rotation policies involving β-lactam/inhibitor combinations, carbapenems and extended-spectrum cephalosporins ± aminoglycosides have been proposed for ICUs.[85] Presumably because of the vast scale of β-lactamase inhibi-

tor prescribing, IRT-producing strains are being increasingly recognised. Reduction in overall antibacterial consumption, together with optimal dose administration regimens rather than simple substitution, should be the ultimate strategy to reduce the emergence of such bacterial resistance.[56,77,86,87]

4. Conclusion

β-Lactam/β-lactamase inhibitor combinations have become widely used antibiotics. With better understanding of their microbiology and pharmacology, and the accumulation of clinical experience, their utility is gradually becoming established and more rational prescribing becomes possible. Besides their unique form of therapeutic efficacy, they may have a role in curbing the emergence of bacterial resistance and, in certain situations, they appear to offer greater cost-effectiveness than antibacterials used hitherto.

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