Journal of Antimicrobial Chemotherapy (1995) **35**, 435–441

For debate

Amoxycillin-clavulanate versus methicillin or isoxazolyl penicillins for treatment of *Staphylococcus aureus* infections

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Introduction

The strategy for β-lactam chemotherapy of *Staphylococcus aureus* infections should be determined by the mechanisms of bacterial resistance to these agents. Staphylococci have developed two major defences against β-lactam bacteriostatic and bactericidal effects. Firstly they may produce penicillinase, which inactivates penicillinase susceptible molecules such as penicillin, amoxycillin and ampicillin and secondly, they may produce penicillin-binding protein 2A (PBP 2A), a new low β-lactam affinity PBP which renders them resistant to methicillin as well as to most other β-lactam antibiotics (Brumfitt & Hamilton-Miller, 1989; Cookson & Phillips, 1990).

Therapeutic strategies to overcome penicillinase production include (i) penicillinase resistant β-lactams such as methicillin, nafcillin, and isoxazolyl penicillins (and also first and second generation cephalosporins) and (ii) penicillinase susceptible antibiotics (such as amoxycillin and ampicillin) combined with penicillinase inhibitors (Table). Methicillin resistant *S. aureus* (MRSA) are less susceptible to β-lactam antibiotics because of the low affinity PBP 2A. Severe MRSA infections are usually treated with non-β-lactam antibiotics such as vancomycin (Brumfitt & Hamilton, 1989). If a β-lactam is to be effective against these bacteria, it would have to resist penicillinase hydrolysis *and* be able to bind and inhibit PBP 2A, as most MRSA isolates produce both these resistance factors. While such an ideal drug has yet to be developed, experiments with amoxycillin combined with the penicillinase inhibitor clavulanate (co-amoxiclav) show that this strategy is effective (Cantoni *et al.*, 1989; Franciolli *et al.*, 1991; Fluckiger *et al.*, 1992; Entenza *et al.*, 1994).

This review attempts to assess the advantages and disadvantages of co-amoxiclav (or other penicillin/penicillinase inhibitor combinations) over methicillin or isoxazolyl penicillins in treatment of *S. aureus* infections.

Methicillin susceptible *S. aureus*

Penicillinase producing *S. aureus* increased dramatically after the introduction of penicillin in the early forties and now over 80% of *S. aureus* isolates produce the enzyme

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0305–7453/95/030435+07 $08.00/0

(Gillespie, May & Skurray, 1985; Moellering, 1993). Penicillinase acylates penicillin molecules in a reaction similar to that of the membrane-bound PBPs involved in cell wall peptidoglycan synthesis which are the primary targets of β-lactams. However, while PBP-acyl-penicillin complexes have a long half-life and cause prolonged inhibition of cell-wall synthesis, penicillinase rapidly hydrolyses its substrate liberating penicillinoic acid and becomes available to inactivate further β-lactam molecules.

To resist penicillinase degradation, penicillin may be modified by addition of bulky side-chains which either decrease the enzyme affinity for the drug, or increase the stability of the penicillin/penicillinase complex (transiently blocking the enzyme), or both mechanisms may operate (Craig, 1992; Moellering, 1993). Such modifications are the basis of methicillin, nafcillin, and isoxazolyl penicillins, which have become the gold standard for treatment of methicillin susceptible staphylococcal infections (Craig, 1992). Their limitations however include reduced activity against a number of organisms, including *S. aureus*. For example, MICs of penicillin G for *Streptococcus pyogenes* or *Streptococcus pneumoniae* are $\leqslant 0{\cdot}01$ mg/L, whereas MICs of methicillin or isoxazolyl penicillins for these organisms are 4–100 fold greater (Table). Similarly, penicillinase-negative *S. aureus* are inhibited by less than 0·05 mg/L of penicillin G, while 10–50 fold more methicillin is needed to obtain the same effect. This decrease in intrinsic activity cannot be overcome by increased drug dosages, as maximum serum concentrations are similar for penicillin G, amoxycillin and ampicillin and for methicillin or isoxazyl penicillins (Craig, 1992). Thus, in the absence of penicillinase, 'simple' penicillin G or amoxycillin may have a 10–50 fold greater therapeutic margin than methicillin or isoxazolyl penicillins for methicillin susceptible staphylococci. Moreover, penicillin G and amoxycillin (and also ampicillin) are less bound to plasma proteins than isoxazolyl penicillins (20–50% and 95%, respectively) (Craig, 1992), a possible advantage at infection sites with impaired drug diffusion such as cerebrospinal fluid or abscesses. Therefore, although methicillin and isoxazolyl penicillins are very effective anti-staphylococcal agents, simpler penicillins might be advantageous if adequately protected from penicillinase degradation.

Penicillinase inhibitors

Effective protection against penicillinase hydrolysis is conferred by irreversible enzyme inactivators such as clavulanic acid, sulbactam, and tazobactam (Bush, 1988; Livermore, 1993), which inhibit a number of β-lactamases including staphylococcal penicillinases. Their β-lactam ring may inhibit bacterial growth at high dosages, but their primary effect is to protect the partner β-lactam from penicillinase degradation. Such drug combinations include co-amoxiclav, ticarcillin/clavulanate, ampicillin/sulbactam and piperacillin/tazobactam, which have proved effective in numerous bacterial infections.

Advantages and disadvantages of co-amoxiclav (or similar combinations) in methicillin-susceptible S. aureus *infections*

We and others have gained experience in the treatment of both experimental and clinical staphylococcal infections with co-amoxiclav. The range of MICs for penicillinase-producing (methicillin sensitive) staphylococci appeared to be lower or equal to that of methicillin or isoxazolyl penicillins (Table). As expected, co-amoxiclav was also effective against a number of organisms which were not inhibited by the penicillinase stable

Table. Susceptibilities of staphylococci and streptococci to penicillinase resistant and penicillinase susceptible penicillins

Bacteria	Minimum inhibitory concentrations (mg/L)[a]					
	Penicillinase resistant		Penicillinase susceptible		Combined with clavulanate	
	methicillin	isoxa pen[b]	penicillin G	amoxycillin	penicillin-clav[c]	co-amoxiclav
S. aureus (Meth-S)						
Penicillinase positive	1	0·25	>64	>64	⩽0·05	0·125
Penicillinase negative	1	0·25	⩽0·05	⩽0·125	⩽0·05	0·125
S. aureus (Meth-R)						
Penicillinase positive	>64	32	>64	>64	4–8	8
Penicillinase negative	>64	32	4	8	4	8
Streptococci						
S. pneumoniae	0·1	0·05	0·01	0·02	ND	0·02
S. pyogenes	0·2	0·02	0·005	0·01	ND	0·01

[a]Data compiled from author's own observations and data presented by Craig (1992). Note that MICs of nafcillin (not reported in the Table) are approximately similar to those of isoxazolyl penicillins.

[b]Isoxazolyl penicillins include oxacillin, cloxacillin, dicloxacillin and flucloxacillin.

[c]Penicillin MICs were performed in the presence of a concentration of 4 mg/L clavulanate.

ND, Not determined.

derivatives, such as Gram-negative and anaerobic bacteria. High tissue concentrations of both components may be achieved after either oral or parenteral administration (Munch, Blaser & Siegenthaler, 1981; Weismeier *et al.*, 1989). Good in-vitro anti-staphylococcal activity is reflected in efficacy *in vivo*, as shown in the experimental model of endocarditis (Cantoni *et al.*, 1989; Franciolli *et al.*, 1991; Fluckiger *et al.*, 1992; Entenza *et al.*, 1994) as well as clinically (Fleisher, Wilmott & Campos, 1983; Camacho *et al.*, 1992; Powers, 1993; Tassler, 1993; Moreillon, 1994). Good results have been obtained with ampicillin/sulbactam in children with staphylococcal skeletal infections (Aronoff *et al.*, 1986; Löffler *et al.*, 1986). On the basis of such results co-amoxiclav has been used for empirical treatment of infections which might involve *S. aureus* (Goldstein *et al.*, 1987; Bass *et al.*, 1993; Moreillon, 1994). It is noteworthy that none of these clinical studies directly compared co-amoxiclav (or similar drug combinations) with methicillin or isoxazolyl penicillins in staphylococcal disease but assessed the efficacy of combinations in a number of clinical infections, many due to staphylococci. Therefore, it is unclear whether co-amoxiclav or similar combinations have any advantage over methicillin or isoxazolyl penicillins and there is a need for further comparative studies.

The potential *advantages* of co-amoxiclav (or similar combinations) can be summarised as follows. (i) If adequately protected from bacterial penicillinase, simpler penicillin molecules might be more effective than methicillin or isoxazolyl penicillins against methicillin sensitive *S. aureus*. This is well established for penicillin G *in vitro* and also tends to be true for amoxycillin and ampicillin (Table). Since agents with lower MICs might be therapeutically more effective, it seems important to compare the efficacy of combination therapy with methicillin or isoxazolyl penicillins in deep-seated staphylococcal infections. (ii) Penicillin G and its amino-derivatives amoxycillin and ampicillin are also active against a variety of other bacteria which may coexist at sites of infection and are not adequately covered by methicillin or isoxazolyl penicillins. This makes co-amoxiclav (and also ampicillin/sulbactam) suitable for empirical treatment of infections which might include *S. aureus* and would not respond to methicillin or isoxazolyl penicillins alone. (iii) Co-amoxiclav is generally well tolerated and has greater bioavailability than methicillin or isoxazolyl penicillins. (iv) Finally, co-amoxiclav is cheaper than isoxazolyl penicillins (there is a price difference of about 20% between these compounds in Switzerland).

The disadvantage of co-amoxiclav is that broad spectrum therapy is best avoided once a specific pathogen has been identified. Over-use of broad spectrum antibacterial agents promotes selection of drug resistance in normal gut flora, and in common with many other physicians, we treat penicillinase-producing (methicillin susceptible) *S. aureus* with isoxazolyl penicillins. In order to outweigh its 'broad spectrum' disadvantage, co-amoxiclav should demonstrate significantly superior anti-staphylococcal activity compared with methicillin or isoxazolyl penicillins *in vivo*. Whether such an advantage exists remains to be determined by valid comparative studies.

A simpler alternative to this dilemma would be to combine clavulanate (or other penicillinase inhibitors) with penicillin G. Penicillin G has excellent intrinsic activity against penicillinase-*negative S. aureus* and is the first choice antibiotic in this now unusual situation. In addition, penicillin G has a much narrower antibacterial spectrum than its amino-derivatives amoxycillin or ampicillin. Therefore, combination of penicillin G with penicillinase inhibitors might emerge as the best antibacterial combination for treating methicillin susceptible staphylococcal infections. Unfortunately this combination is not yet available and manufacturers should consider such a formulation.

Methicillin resistant *S. aureus* (MRSA)

Methicillin resistant (PBP 2A-producing) staphylococci emerged in the sixties, in response to the introduction of new penicillinase stable β-lactams such as methicillin (Brumfitt & Hamilton-Miller, 1990). The initial increase in MRSA was relatively slow, perhaps because the PBP 2A (*mec*) gene is chromosomal and less transmissible than penicillinase genes, which reside on transferable plasmids or transposons. Nevertheless, MRSA has steadily increased over the last decade and now represents up to 40% of staphylococcal isolates in certain hospitals worldwide. Moreover, MRSA are also resistant to most other antibiotics, posing a challenge to modern antimicrobial chemotherapy (Brumfitt & Hamilton-Miller, 1989; Cookson & Phillips, 1990).

Interestingly, traditional β-lactams such as penicillin G, amoxycillin and ampicillin have relatively good PBP 2A affinity and also relatively low MICs for penicillinase negative MRSA isolates (Table) (Chambers & Sachdeva, 1990; Franciolli *et al.*, 1881). These antibiotics must be combined with penicillinase inhibitors to avoid degradation by penicillinase producers. Co-amoxiclav and ampicillin/sulbactam appeared to fulfil these conditions both *in vitro* and *in vivo*, as shown in the experimental model of endocarditis and in preliminary human studies. In animals, amoxycillin alone cured experimental endocarditis due to penicillinase negative MRSA, whereas cloxacillin was ineffective (Franciolli *et al.*, 1991). Amoxycillin alone failed against penicillinase producing parent strains as it was hydrolysed by bacterial β-lactamases. However, efficacy could be fully restored by combining amoxycillin with clavulanate. These experimental results were confirmed using other MRSA isolates (which expressed both 'heterogeneous' and 'homogeneous' resistance to methicillin) as well as with methicillin resistant *S. epidermidis* (Entenza *et al.*, 1994) and also using ampicillin/sulbactam (Hirano & Bayer, 1991 and unpublished observation).

Two preliminary reports have suggested that co-amoxiclav and ampicillin/sulbactam might be effective clinically against MRSA infections (Andreoni *et al.*, 1991; Nicolas, Kitzis & Karim, 1993). In a pilot study, Andreoni *et al.* (1991) treated 19 patients with methicillin resistant staphylococcal skin and soft tissue infections (15 due to MRSA) with high parenteral doses (9–12 g/day) of ampicillin/sulbactam for 9–25 days. Clinical and bacteriological responses were excellent and organisms were eradicated in 89% of cases. In another study, Nicolas *et al.* (1993) successfully treated 14/17 urinary tract infections due to MRSA (in urology patients) with oral co-amoxiclav. While this success was related to the high urinary concentration of the drug, it suggests that these combinations can be effective against some MRSA infections.

It is noteworthy however that these were uncontrolled pilot studies undertaken without comparison with standard anti-MRSA drugs such as vancomycin and β-lactam treatment of MRSA is not currently advocated, at least until these results are confirmed by comparative studies.

Conclusion

These experimental and clinical data demonstrate that co-amoxiclav or similar drug combinations (such as ampicillin/sulbactam) are effective against methicillin susceptible *S. aureus*. In addition, these antibiotics could perhaps also be effective therapy for certain methicillin resistant staphylococcal infections. The broad antibacterial spectrum and anti-staphylococcal activity of co-amoxiclav make it suitable for empirical therapy of

infections which may involve staphylococci. However, the possible role of co-amoxiclav in preference to methicillin or isoxazolyl penicillins for long term therapy of methicillin susceptible staphylococci remains uncertain because there are as yet no comparative clinical studies to resolve the issue.

Such studies would be worthwhile because co-amoxiclav (and also ampicillin/sulbactam) may be more active than methicillin or isoxazolyl penicillins against staphylococci and also have better bioavailability. An even better choice would be penicillin G combined with a penicillinase inhibitor, because it would have a narrower antibacterial spectrum and be more active than co-amoxiclav against staphylococci. Finally, further studies to compare the efficacy of high dose co-amoxiclav (or ampicillin/sulbactam) with standard anti-MRSA therapy would be worth considering initially in non-life-threatening infections. In view of the therapeutic problems posed by these organisms today, these are potentially important investigations.

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(Received 8 August 1994; accepted 19 October 1994)