UCLA Health System

Aminopenicillins for the treatmen of Vancomycin-resistant Enterococcal Urinary Tract Infections

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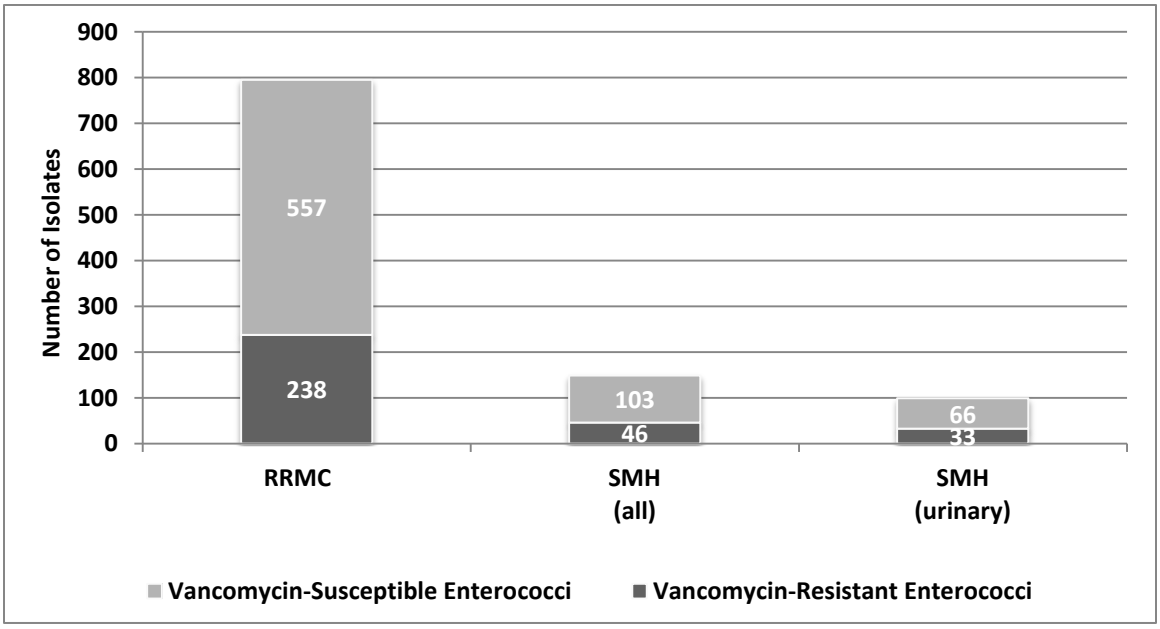
I. Background:

Vancomycin-resistant enterococcal (VRE) infections, and in particular, VRE bacteriuria, present a large burden to patients, providers, and the overall healthcare system. According to the 2013 UCLA Health System Antimicrobial Susceptibility Summary, approximately one-third of all enterococcal isolates at both Ronald Reagan Medical Center (RRMC) and Santa Monical Hospital (SMH) were resistant to vancomycin. This rate of vancomycin-resistance is consistent with National Healthcare Safety Network data from 2006-2007 [Hidron 2008].

Figure 1:

Vancomycin-Susceptible and Vancomycin-Resistant Enterococcus at UCLA Medical Center



Stewarding the antimicrobial management of VRE bacteriuria presents an important opportunity to direct appropriate antimicrobial use. A retrospective evaluation of enterococcal bacteriuria at two institutions in Houston, TX (MD Anderson and the Veteran's Administration) found that one third of asymptomatic bacteriuria was inappropriately treated with antibiotics [Lin 2012]. The University of California, Davis Medical Center reported an excess of $50,000 in drug-acquisition costs of linezolid and daptomycin alone, associated with over-treating VRE bacteriuria during a 3-year period [Heintz 2012].

II. Proposed Treatment Approach:

The treatment of choice for VRE urinary tract infections is ampicillin, when the organism is susceptible to this antibiotic [Heintz 2010]. For VRE resistant to ampicillin, clinical guidance suggests use of alternative therapy including linezolid, daptomycin, doxycycline, nitrofurantoin, or fosfomycin [Heintz 2010]. In the case of urine isolates, the clinician must keep in mind that significantly higher concentrations of ampicillin are achieved in this environment compared to the serum.

A. *Pharmacokinetic/Pharmacodynamic data*

Seventy-five percent of the dose of parentally adminstered ampicillin is excreted unchanged in the urine. Similarly, between 58 – 68% of amoxicillin is excreted unchanged in the urine upon oral dosing [Kucers' 2010, Cole 1978]. According to the Clinical Laboratory Standards Institute (CLSI), the minimum inhibitory concentration (MIC) breakpoint to determine enterococcal susceptibility to ampicillin is < 8 mcg/mL [CLSI 2012]. The target pharmacokinetic/pharmacodynamic parameter to maximize bactericidal activity of aminopenicillins is duration of time the non-protein-bound antibiotic concentration exceeds the organism MIC. The goal breakpoint for beta-lactam antibiotics is time exceeding the MIC over ≥50% of the dosing interval [Lodise 2004].

Urinary concentrations achieved after a 500 mg oral dose of ampicillin range between 250 – 1000 mcg/mL; those reported for the same dose of amoxicillin range from 115 – 1850 mcg/mL [Kucers' 2010]. Drug concentrations have been demonstrated to remain > 100 mcg/mL over a 4-hour interval after a single 250 mg dose of ampicillin or amoxicillin in healthy volunteers [Cole 1978].

Applying this information to clinical practice: After a 500 mg dose, concentrations of either ampicillin or amoxicillin would be reliably expected to exceed the MIC for a duration of 4 – 6 hours for urinary VRE isolates with MICs ≤ 128 mcg/mL.

Table 1: Urine drug concentrations achieved upon oral dosing of ampicillin and amoxicillin[1]

Aminopenicillin (500mg PO)	Urine Concentration (mcg/mL)	Serum half-life (h)[2]
Ampicillin	**250 – 1000**	**1 – 2 hours**
Amoxicillin	**115 – 1850**	**1 – 1.5 hours**

[1]The CLSI susceptibility breakpoint for enterococcus and ampicillin is < 8 mcg/mL

[2]In subjects with unimpaired renal function

The use of urinary inhibitory concentrations to achieve clinical success is not a new concept. McCabe and Jackson demonstrated in 1965 that serum inhibitory antibiotic concentrations were not required for successful treatment of UTIs as long as urinary inhibitory concentrations were achieved [McCabe and Jackson 1965]. These findings were corroborated by Stamey and colleagues in 1974, and provide a clinical pharmacokinetic proof of concept to support this treatment strategy [Stamey 1974].

B. *Clinical Data*

The data for use of amoxicillin or ampicillin to treat VRE bacteriuria resistant to ampicillin are limited. A single-center, retrospective review of aminopenicillin use for VRE UTIs was presented at ICAAC in 2012 [Shultz 2012]. Among 70 subjects evaluated with urine cultures positive for VRE and at least one clinical sign or symptom of a UTI, 91.4% and 90% demonstrated clinical cure and microbiologic eradication respectively upon treatment with ampicillin [Shultz 2012]. Overall, there were 71 VRE isolates: 64 *E.* faecium and 7 *E. faecalis.* All but 1 *E. faecium* isolate was deemed resistant to ampicillin whereas only 1 *E. faecalis* isolate was found to be resistant to ampicillin [Shultz 2012]. Forty-eight patients had foley catheters which were removed in 31 (71%) of the cases evaluated. Patients whose catheters remained in place (N=14) demonstrated a cure rate of only 57% [Shultz 2012].

III. Summary and Conclusions

The strategy to use aminopenicillins to treat VRE UTIs with an MIC ≤ 128 mcg/mL is supported by pharmacokinetic data. However, clinical data describing use of aminopenicillins in patients with VRE UTIs documented as resistant to ampicillin are limited to research abstracts from national and international meetings. Thus, the selection of patients in whom this strategy may be used should be cautious and reserved for uncomplicated, luminal, urinary tract infections that do not involve the renal parenchyma. Use of pharmacotherapy should not preclude addressing the source of infection and removing and replacing indwelling urinary catheters.

IV. References:

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