LINEZOLID VS. VANCOMYCIN: AN EVALUATION IN THE TREATMENT OF SKIN AND SOFT TISSUE INFECTIONS AND HOSPITAL-ACQUIRED PNEUMONIA CAUSED BY METHICILLIN-RESISTANT *S. AUREUS* (MRSA)

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Microbial resistance to antibiotics represents one of the most common reasons for the failure to cure an infection. Methicillin-resistant *S. aureus* (MRSA), first detected after the introduction of methicillin in the early 1960's, has emerged as the most commonly identified antibiotic resistant pathogen in hospitals across the United States.[1] According to the Centers for Disease Control and Prevention, the prevalence of MRSA was 57% in US intensive care units in 2002; this represents an increase of 30-40% from the mid-1990s.[2] MRSA is not strictly a nosocomial pathogen; many genetically distinct strains have now been identified in the community among healthy patients without predisposing factors for MRSA acquisition.[1] The high incidence and continuously growing rate of hospital-acquired (HA) MRSA and now community-acquired (CA) MRSA is a major threat and poses a difficult challenge for health-care professionals.

MRSA is one of the leading pathogens found in both nosocomial pneumonia and skin and soft tissue infections (SSTIs).[3] The prevalence of MRSA in ventilator-associated pneumonia (VAP) constitutes about 50% of the episodes caused by *S. aureus*.[4] Hospital-acquired Pneumonia (HAP) is estimated to account for almost half of infections found in the ICU and approximately 60% of deaths from nosocomial infections.[5] Skin and soft tissue infections are another significant cause of morbidity and mortality in hospitals. Reports from the SENTRY Antimicrobial Surveillance Program reported a methicillin resistance rate of 30% among *S. aureus* isolates in the United States between 1997 and 1999 in skin and soft tissue infections.[6] Methicillin resistance in *S. aureus* confers resistance to B-lactams, in addition to macrolides, fluoroquinolones, tetracyclines, lincosamides, and aminoglycosides.[3] Treatments effective against MRSA include quinupristin/dalfopristin, daptomycin, oritavancin, and tigecycline.[1] Vancomcyin has been the traditional drug used for nosocomial pneumonia or complicated skin and soft tissue infections (cSSTIs) caused by gram-positive resistant organisms.[3] Linezolid, an alternative agent, has generally been reserved for the treatment of serious infections due to its high cost and hematologic concerns. The purpose of this paper is to compare the efficacy, tolerability, and cost of vancomycin and linezolid in the treatment of nosocomial pneumonia and skin and soft tissue infections caused by MRSA.

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Vancomycin

Vancomycin is a glycopeptide used to treat serious infections caused by gram-positive bacteria. [7] After increasing resistance rates to oxacillin and the introduction of MRSA, the use of vancomycin in clinical practice skyrocketed. [8] Vancomycin inhibits cell wall synthesis by binding to the D-alanlyl-D-alanine C-terminus of the nascent murein monomer, inhibiting peptidoglycan synthesis. [9] Vancomycin is slowly bactericidal, with the degree of killing dependent upon the time that the serum concentration is above the organism's minimum inhibitory concentration (MIC). Vancomycin does not exhibit a post-antibiotic effect. *In vitro* studies demonstrate that vancomycin exhibits slower bactericidal activity compared to B-lactams in methicillin-susceptible *S. aureus*. [7] The concentration of vancomycin required to inhibit most strains of *S. aureus* is typically between 0.5 and 2 mg/L. According to the Clinical and Laboratory Standards Institute (CLSI), *S. aureus* isolates with vancomycin MICs of 4 mg/L or less should be considered susceptible, isolates with vancomycin MICs between 8 and 16 mg/L are vancomycin-intermediate, and isolates with vancomycin MICs $\geq$ 32 mg/L are considered vancomycin-resistant. [10] The emergence of *S. aureus* strains intermediate or resistant to vancomycin has led to many treatment failures.

Some pharmacokinetic properties of vancomycin have contributed to its relatively high incidence of treatment failure in VAP and SSTIs. Table 1 shows the clinical success rates of vancomycin in various studies. [11-14] Vancomycin has poor tissue penetration, especially into the lungs. [15] Concentrations of vancomycin in the epithelial lining fluid (ELF) do not reach 20% of the plasma concentration. [16] In a study by Cruciani et al., an intravenous (IV) infusion of 1 g of vancomycin over 1 h failed to achieve sustained lung concentrations above the MIC for susceptible *S. aureus* over a 12 h dosing interval. [17] The difficulties in obtaining adequate local serum concentrations have led to higher doses and intense pharmacokinetic monitoring to improve efficacy and avoid toxicity. Studies have evaluated the potential of higher trough concentrations of 15-20 mg/L to enhance efficacy with vancomycin. A continuous IV infusion of vancomycin has also been studied. However, there is no clear consensus in the literature supporting elevated trough concentrations of 15-20 mg/L or continuous IV infusion. Higher trough concentrations of vancomycin may increase the risk of nephrotoxocity, particularly if the patient is also receiving aminoglycosides. [18]

Vancomycin's high molecular weight contributes to poor oral absorption. Therefore, vancomycin must be administered IV for systemic infections. IV access typically requires hospitalization and is associated with additional resources and increased costs. It also enhances the risk of phlebitis, puncture accidents, as well as catheter-related and hospital-acquired bloodstream. [3]

Resistance

An emergence of staphylococci intermediate or resistant to vancomycin has led to failures in nosocomial pneumonia and SSTIs caused by MRSA. The first clinical isolate of *S. aureus* with reduced susceptibility to vancomycin was reported in 1997 from Japan. These isolates were known as vancomycin-intermediate *S. aureus* (VISA), also known as glycopeptide-intermediate *S. aureus* (GISA), since MICs ranged from 8-16 mg/L. [19] VISA strains produce an excess amount of non-cross-linked D-alanyl-D-alanine residues, which bind to vancomycin molecules and sequester them. This prevents vancomycin from reaching its target site, leading to treatment fail-

Table 1. Clinical success of vancomycin in MRSA nosocomial pneumonia

Trials	N	Dose	Infection	Success rate
Stevens et al [11]	220	1 g vancomycin IV q 12 h	HAP	53.8%
Fagon et al[12]	20	1 g vancomycin IV q 12 h	HAP	40%
Wunderink et al[13]	54	1 g vancomycin IV q 12 h	HAP	35.5%
Kollef et al[14]	91	1 g vancomycin IV q 12 h plus aztreonam	VAP	21%

N = number of patients

ures. VISA strains also have a thicker cell wall with increased amounts of peptidoglycan that further obstructs the movement of vancomycin molecules.[19] Heteroresistant VISA (hVISA) also demonstrates decreased susceptibility to vancomycin and is considered to be a precursor to VISA. hVISA is more common, and now accounts for up to 26% of MRSA isolates in Japan.[8] Vancomycin MICs in hVISA are in the susceptible range ($\leq$ 4 mg/L); however subpopulations have MICs > 4 mg/L exhibiting reduced susceptibility. There are no standardized methods to identify hVISA, which makes predicting treatment failures difficult. Several published studies show vancomycin to be ineffective for hVISA strains.[8] Vancomycin-resistant *S. aureus* (VRSA) is rare and is defined as an MIC $\geq$ 32 mg/L. To date, there have been 4 cases of VRSA. All cases have been in the United States with each isolate from a single patient: 2 have been from Michigan, one from Pennsylvania, and one from New York.[10] VRSA strains obtain their resistance by conjugal transfer of plasmids containing the vanA operon from vancomycin-resistant *Enterococcus faecalis.*[10] Common screening methods, such as Vitek® or Microscan®, are not effective, with about two-thirds of confirmed VRSA isolates not reliably detected by automated testing systems.[10]

The development of resistance to vancomycin in *S. aureus* has been associated with prolonged exposure to low serum concentrations of the drug.[20] Physicians tend to underdose vancomycin in patients with renal failure.[18] Moise et al. found a significant association between decreased creatinine clearance and vancomycin treatment failure.[21] The majority of cases of VISA have occurred in patients receiving prolonged, suboptimal, or repeated courses of vancomcyin or in patients receiving peritoneal or hemodialysis.[20] In addition, a polymorphism has been identified among VISA and hVISA strains in the accessory gene regulator (agr). The agr operon in *S. aureus* controls many virulence pathways. The agr group II polymorphism was found to be an independent predictor of vancomycin failure in patients with MRSA infection.[21]

Linezolid

Linezolid (Zyvox®), an oxazolidinone, entered the US market on April 18, 2000.[22] Its ability to target both susceptible and multi-drug resistant strains makes it a highly effective agent to treat both HAP and CAP, as well as SSTIs. Linezolid provides inhibitory activity against most gram-positive cocci, such as staphylococci, streptococci, and enterococci. This includes resistant *S. pneumoniae*, staphylococci resistant to methicillin, vancomycin, and B-lactam antibiotics, and vancomycin-resistant enterococci (VRE).[23] *In vitro* studies show susceptible MICs for staphylococci are between 0.5 and 4 mg/L.[24] Linezolid is bacteriostatic for *S. aureus*. Unlike vancomycin, it exhibits a post-antibiotic effect of 3-4 hours.[15] Linezolid exerts its antimicrobial effects by preventing formation of the 70 S initiation complex of ribosomes. Because of its mechanism of action, there is virtually no cross-resistance between linezolid and other classes of antibiotics (lincosamides, macrolides, streptogramins, and chloramphenicol) affecting ribosome mediated protein synthesis.[23] Resistance to linezolid is extremely rare. According to the LEADER National Surveillance Study in 2004, all 2,872 isolated organisms of *S. aureus* showed susceptibility to linezolid. [25]

The pharmacokinetics of linezolid give it an advantage over vancomycin. Linezolid is 100% bioavailable and can be administered both orally and parentally. [3] Patients can transition to oral therapy with no dosage adjustments, which may facilitate earlier discharge.[23] Linezolid has excellent tissue penetration. Protein binding with linezolid is 31%, which provides free drug concentrations of > 40 mg/L in the ELF.[15] In Conti et al., following an IV or oral dose, plasma concentrations were 15-20 mg/L, while bronchoalveolar lavage concentrations (BLC) exceeded 64 mg/L.[26] Metabolism of linezolid is through non-enzymatic oxidation of the morpholine ring and is not dependent on hepatic enzyme action. No dosage adjustments are necessary for patients with hepatic or renal dysfunction.[23]

Linezolid appears to be safe and well tolerated in clinical trials. Common drug-related adverse events include diarrhea, nausea, and headache, and are typically of limited duration. Hematologic events (anemia, thrombocytopenia, leukopenia, and neutropenia) have been reported; decreased platelet counts are often associated with prolonged treatment courses of more than 14 days. In phase III studies, 2.4% of patients treated with linezolid and 1.5% of patients treated with comparator drugs developed reversible thrombocytopenia.[27] Other serious adverse effects reported with linezolid include lactic acidosis, pseudomembranous colitis, and peripheral and optic neuropathy.[23]

Table 2: Clinical trial summaries

Trial	N	Study Design	Infec-tion	Treatment	Result
Kollef et al[14]	544 (91 in MRSA cohort)	MN, R Analysis of 2 DB, Ra studies	VAP	Linezolid 600 mg IV q 12 or vancomycin 1 g IV q 12 for 7-21 days plus aztreonam	Linezolid had higher rates of clinical cure (62.2 vs 21.1%), survival (84.1% vs 61.1%) and eradication (60.5 vs 23%)
Weigelt et al[28]	1,180	Ra, OL,CC, MN, MC	cSSTI	Vancomycin 1 g q 12 IV or linezolid 600 mg q 12 PO or IV.	Response to treatment was higher in linezolid group (88%) compared to vancomycin group (67%).
Wunderink et al[13]	396	RA, DB	HAP	Linezolid 600 mg q 12 IV or vancomycin 1 g q 12 IV plus aztreonam for 7-21days	Linezolid was equal in efficacy and tolerability compared to vancomy-cin. Clinical cure rates (67.9% vs 64.9%)
Wunderink et al[29]	1,019 (160 in MRSA cohort)	MN, R Analysis of 2 DB, Ra studies	HAP	Vancomycin 1 g IV q 12 or 600 mg linezolid IV q 12 plus aztreonam	Clinical cure rates were higher with linezolid (59% vs 35.5 %), survival analysis was 85% vs 67%
Weigelt et al[30]	135	Ra, OL, CC,MN, MC	cSSTIs	Vancomycin 1 g q 12 IV or linezolid 600 mg PO/ IV q 12 for 7-21 days	Microbiological success was 87% with linezolid vs 48% with vancom-cyin. (CI 16.51-60.27, p=0.002)

Ra=Randomized, DB=Double-blind, R=Retrospective, OL=Open-Label, CC=Comparator Controlled, MN=Multi-National, MC=Multi-Center

Clinical Trials

Numerous head-to-head clinical trials have been conducted comparing the clinical efficacy of linezolid and vancomycin to treat both HAP and cSSTIs (table 2). Wunderink et al. evaluated 1,019 patients with suspected nosocomial pneumonia (160 patients had documented MRSA pneumonia in the MRSA subset) and randomized them to receive either 1 g of vancomycin every 12 h or 600 mg of line-zolid every 12 h, each with aztreonam. Clinical cure rates with linezolid were 59% vs 35.5% treated with vancomycin (p<0.01). Kaplan-Meier survival rates were 85% for linezolid vs. 67% with vancomycin (p=0.05).[13] Weigelt et al. randomized 1,180 patients with suspected or proven MRSA infections to receive vancomycin 1 g every 12 h IV or linezolid 600 mg every 12 h administered either orally or IV. The primary outcome, defined as clinical response to treatment, was significantly higher in the linezolid group (88.6%) compared to the vancomycin group (66.9%) at the Test of Cure (TOC) visit for MRSA infections (p<0.001).[28]

Adverse Effects

Table 3 lists the frequency of drug related adverse events in the study by Weigelt et al.[28] Line-zolid and vancomycin reported similar drug-related events. In the vancomycin arm, rash, phlebitis, ana-phylaxis, and drug related allergic reactions were the most common adverse effects, while gastrointestinal disturbances (nausea, diarrhea) and thrombocyto-penia (3.5%) occurred more frequently in the line-zolid group. No difference between the two groups

Table 3. Comparison of adverse events[28]

Adverse Events	Linezolid N=592 (%)	Vancomycin N=588 (%)
Serious Adverse Events	131 (22.1)	121 (20.6)
Drug-Related Events	2 (<1)	8 (1.4)
Most Common events (>1%)		
Anemia	7 (1.2)	10 (1.7)
Diarrhea	31(5.2)	9 (1.5)
Headache	10 (1.7)	4 (0.7)
Nausea	24 (4.1)	8 (1.4)
Pruritis	6 (1.0)	10 (1.7)
Rash	3 (0.5)	16 (2.7)
Thrombocyto-penia	21 (3.5)	0
Vomiting	8 (1.4)	5 (0.9)

N = number of events

was observed in the frequency of adverse events leading to drug discontinuation.[28]

Cost

Linezolid has been avoided due its high expense. The average retail cost of Zyvox® surveyed from three local pharmacies in Gainesville is $72.78 for one 600 mg tablet. For a 1 g vial of generic IV vancomycin, the average retail cost from local pharmacies is $15.39. However, clinical studies demonstrate that linezolid is more cost effective in the long run. The oral form of linezolid has led to decreased costs versus the intravenous administration of vancomycin. Shah et al. evaluated the direct cost of vancomycin in MRSA infections. After including secondary expenses (monitoring, drug administration, professional involvement, and adverse events), each dose of vancomycin generated an estimate increase in cost between $23 and $43.[31] Clinical trials with oral linezolid have substantially decreased hospital costs by reducing length of stay (LOS), reducing resources associated with intravenous therapy, and facilitating earlier hospital discharges. Li et al., in a phase III, open-label, comparator-controlled, multicenter, multinational study, randomized 230 patients to receive linezolid 600 mg twice a day vs 1 g vancomycin IV twice a day for the treatment of cSSTIs. LOS was shorter with linezolid than vancomycin (9 vs 14 days), and the estimated odds for hospital discharge in the linezolid group was 1.87 times the estimated odds of discharge in the vancomycin group.[32] Sharpe et al. studied 60 patients requiring surgical intervention for MRSA infected skin lesions. Patients were randomized to receive oral linezolid 600 mg every 12 h or 1 g vancomycin IV every 12 h for 7-21 days. LOS was 3 days shorter with linezolid and saved $6,438 per patient in total hospital charges. Outpatient charges with linezolid also resulted in a savings of $388 per patient.[33]

Summary

Vancomycin has remained the drug of choice for the treatment of MRSA, particularly in hospital-acquired pneumonia, and skin and soft tissue infections. However, due to several parameters associated with the pharmacokinetics of vancomycin, as well as increasing prevalence of hVISA and VISA, treatment failures have been observed. Linezolid, which is available orally, is very effective in treating MRSA intermediate or resistant to vancomycin. Clinical trials show linezolid to have superior clinical outcomes, increased cost effectiveness, and favorable tolerability compared to vancomycin.

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