THE CHILDREN'S MEDICAL CENTER OF DAYTON

Pediatric Clips

Treatment of serious staphylococcal infections: appropriate use of vancomycin

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Pediatric Clips *from The Children's Medical Center of Dayton are quick reviews of common pediatric conditions.*

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Infections caused by *Staphylococcus aureus* account for a large proportion of children seen in both the ambulatory setting and in the hospital. The second most common inpatient diagnosis at The Children's Medical Center of Dayton in 2008 was skin and soft tissue infection. Most of these infections are secondary to methicillin-resistant *Staphylococcus aureus* (MRSA). While many abscessed cutaneous infections will improve with only surgical drainage, specific antibiotic therapy alone or in combination with surgical care is necessary to guarantee recovery from these frequently serious infections in many children. Unfortunately, the antibiotic armamentarium to successfully treat these infections is becoming increasingly limited.

Vancomycin has been considered the gold standard of therapy for serious methicillin-resistant staphylococcal infections. A number of studies have noted, however, some diminished vancomycin efficacy due to increasing resistance among MRSA strains. Infections caused by strains of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) have been seen but are rare. Heteroresistant VISA (hVISA) are comprised of bacterial subpopulations with both susceptible and resistant strains. Laboratory methods to identify hVISA have not been standardized as of yet.

Across the country, reports in adults have documented reduced clinical efficacy of vancomycin in the treatment of MRSA infections in which the isolates have increased minimum inhibitory concentrations (MICs) but are still susceptible. In the past a typical *S. aureus* MIC for vancomycin was 0.25-0.5 µg/mL, and recently MICs of 1 µg/mL or higher have been seen, a phenomenon known as MIC creep. Therapeutic failure in some of these cases has occurred despite MICs within the susceptible range (MIC <2 µg/mL). Rates of resistance are growing; therefore, the Food and Drug Administration (FDA) in 2008 lowered the laboratory MIC breakpoints for vancomycin in the treatment of *S. aureus* infections. (Table 1).

Table 1

Vancomycin Susceptibility Breakpoints Minimum Inhibitory Concentration (MIC) (µg/mL)		
Susceptible (S)	Intermediate (I)	Resistant (R)
<2	4-8	>16

2009 LABORATORY RESULTS

Dayton Children's microbiology laboratory identified 2165 isolates of *S. aureus*, 55 percent of which were resistant to methicillin (MRSA). As a whole, vancomycin MIC values remained relatively low among these organisms, with 100 percent of isolates having an MIC value of < 1 µg/mL and 70 percent having MICs of < 0.5 µg/mL. Clindamycin resistance among all *Staphylococcus aureus* isolates was 27 percent (of which 13.5 percent displayed inducible clindamycin resistance). Among MRSA, clindamycin resistance was 31 percent. Such a high incidence of resistance to this antibiotic should prompt very careful consideration when empirically treating MRSA infections with this agent. Trimethoprim/Sulfamethoxazole continued to be an effective choice for select infections as 92 percent of all organisms remained susceptible.

TREATMENT RECOMMENDATIONS

While other antibiotics are available to treat resistant staphylococcal infections, vancomycin continues to be the agent of choice. Appropriate dosing with this antibiotic, however, can at times be a challenge. Vancomycin dosing for children has been referenced as 40 mg/kg/day in divided doses for decades. The emergence of bacteria increasingly resistant to vancomycin, however, prompts a reevaluation of these recommendations. In one study evaluating vancomycin dosing in children with invasive MRSA infections, current dosing recommendations of 40 mg/kg/day in children did not achieve adequate target levels for organisms with an MIC of >1 µg/mL. The authors concluded:

- empiric vancomycin dosing for invasive MRSA should be 60 mg/kg/day (15 mg/kg/dose every six hours),
- active surveillance and knowledge of MIC trends is important in initial dose considerations, and
- further pharmacokinetic studies in children are needed to optimize vancomycin dosing.

Trough level monitoring of vancomycin seems to be the best predictor of efficacy. Trough levels should be drawn at steady state just prior to a dose. Steady state is usually obtained by the fourth dose of vancomycin. In the past trough levels of 5-10 µg/mL were considered adequate to treat most infections. With the emergence of MRSA with increased MICs to vancomycin, trough level targets are increasing. Many institutions are now using a target trough range of 5-15 µg/mL. In pediatric patients with good renal function, such higher trough levels are difficult to attain even with 60 mg/kg/day. Vancomycin dosing may need to be increased to 80 mg/kg/day especially in MRSA infections with MICs ≥ 1 mcg/ml. Peak levels of vancomycin have not been shown to correlate with efficacy or toxicity.

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The monitoring of trough vancomycin levels is recommended for patients receiving aggressive therapy and for patients either at risk of nephrotoxicity or in those with renal impairment. Patients receiving empiric therapy with normal renal function do not routinely require trough antibiotic levels unless it is determined that therapy with vancomycin will continue for more than three to five days. Patients continued on vancomycin for long-term therapy (greater than 10-14 days) may need weekly trough monitoring. Serum creatinine concentrations should be monitored to detect potential nephrotoxicity.

It is important to treat the patient and not the laboratory value. If a patient is clinically improving on vancomycin and the MIC of the organism is <1 µg/mL lower trough levels are adequate. If the patient is not improving and the MIC of the organism is ≥ 1 µg/mL treatment with an alternative antibiotic may be necessary. Additional antimicrobial agents to treat these serious infections are currently under investigation.

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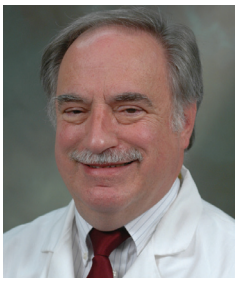
FEATURED SPECIALISTS

SHERMAN ALTER, MD, serves as medical director for the infectious disease department and Almost Home Unit at Dayton Children's. He completed his fellowship in infectious disease at Cincinnati Children's Hospital Medical Center and received his medical degree from The Ohio State University College of Medicine. He is an associate professor of pediatrics at Wright State University Boonshoft School of Medicine.



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