Antibiotic Practice Change to Curtail Linezolid Use in Pediatric Hospitalized Patients in Hawai‘i with Uncomplicated Skin and Soft Tissue Infections

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Abstract

Antimicrobial resistance affects health care providers' choice of antibiotics in the treatment of skin and soft tissue infections (SSTIs). Based on local antibiotic susceptibility data showing high clindamycin resistance and high MRSA prevalence, a change in antibiotic regimen for children hospitalized for uncomplicated SSTIs was instituted in an attempt to curb the use of linezolid. A retrospective chart review was performed on 278 pediatric patients with uncomplicated SSTIs hospitalized at Kapi'olani Medical Center for Women and Children in Hawai'i from May 2014 to April 2015 and November 2015 to October 2016. Data consisted of 12 months of baseline data and 12 months of data post-implementation of an antibiotic combination regimen of 2 widely-used antibiotics: high-dose cefazolin and high-dose clindamycin. Practitioners were encouraged to use cefazolin alone if clinical suspicion was high for single-organism infection with group A streptococcus. *The measured outcomes included initial antibiotic, switch in antibiotic, and length of stay. The use of the combination of cefazolin and clindamycin as the initial treatment, compared with prior practice of monotherapy with clindamycin or cephazolin, was associated with fewer patients started on linezolid (*P=.03*), no increase in patients switching to linezolid (*P=.97*), and no significant change in length of stay (*P=.06*). When clindamycin resistance and MRSA prevalence are both elevated, the combination of cefazolin and clindamycin is an option that can help with antibiotic stewardship to decrease the use of linezolid.*

Keywords

Antibiotic resistance, Hawai'i, Pediatrics, Skin and soft tissue infection, Staphylococcus*,* Streptococcus

Abbreviations

GAS = group A Streptococcus
MRSA = methicillin-resistant Staphylococcus aureus
MSSA = methicillin-susceptible Staphylococcus aureus
SA = Staphylococcus aureus
SD = standard deviation
SSTI = skin and soft tissue infection

Introduction

Antimicrobial resistance is of increasing global concern. Changes in resistance patterns require adjustments in the choice of antibiotics for a variety of infections, including the treatment of uncomplicated skin and soft tissue infections (SSTI) typically caused by *Staphylococcus aureus* (SA) and group A *Streptococcus* (GAS). The rise in methicillin-resistant *Staphylococcus aureus* (MRSA) between 1990 to 2005 led to MRSA infection becoming more common than methicillin-susceptible *Staphylococcus aureus* (MSSA) infections.[1] For MRSA coverage, clindamycin became a widely-used antibiotic for treating uncomplicated SSTIs in children. Following increasing clindamycin use, increasing clindamycin resistance was soon noted, particularly in MRSA isolates.[2] Prior to 2010, MRSA predominance appeared to peak, and since then it has been decreasing.[3] The prevalence of clindamycin-resistant GAS has been known to vary with time and location with US rates ranging from 4%-41% since the early 2000s.[4]

In Hawai‘i, methicillin and clindamycin resistance patterns of SA initially followed similar increasing trends. Antibiograms at Hawai‘i's children's hospital, Kapi‘olani Medical Center for Women and Children, showed that MRSA accounted for 23%-31% of SA isolates since 2012, and 27% in 2018. Clindamycin-resistant MRSA reached a peak at 36% in 2014 and decreased to 27% for the past 2 years, and clindamycin-resistant MSSA has fluctuated between 18-26% since 2012, and was 21% in 2018.[5] Testing of GAS for clindamycin-susceptibility began in 2015 at the hospital; since then, GAS clindamycin-resistance ranged from 3%-14%, and was 10% in 2018.

Vancomycin and linezolid are 2 of the very limited number of antibiotics used to treat clindamycin-resistant MRSA. Both have high costs associated with them, linezolid due to the higher drug cost and vancomycin due to costs for monitoring and administration. Vancomycin is only effective for SSTIs when given intravenously. Linezolid has the added benefit of an oral formulation that has equivalent bioavailability as the intravenous formulation. With increasing use, vancomycin and linezolid resistance have been reported.[6-8]

Antimicrobial stewardship has become a nationwide mission. Many organizations including the Centers for Medicare and Medicaid Services have rallied to the call for more appropriate use of antimicrobials to decrease the development of multidrug-resistant organisms, which can result in increased morbidity and mortality and increased health care costs. Starting in 2016, Kapi‘olani Medical Center for Women and Children began developing its own antimicrobial stewardship program. One focus of this program was also on linezolid.

Prior to 2015, the majority of pediatric patients admitted to Kapi‘olani Medical Center for Women and Children for uncomplicated SSTIs were treated with clindamycin alone. In cases of presumed outpatient clindamycin failure, patients were started on vancomycin or linezolid. Linezolid, at times, was preferred due

to concern for difficulties in attaining therapeutic vancomycin levels. Patients who were on vancomycin or linezolid in the hospital and had no positive cultures were typically discharged on oral linezolid. The definition of clindamycin failure was not well-identified and some patients considered to have clindamycin failure had received less than 48 hours of clindamycin. It was hypothesized that some of these presumed failures were due to inadequate duration on clindamycin, clindamycin-resistant GAS, or clindamycin-resistant MSSA infections, and that these "failures" might have been adequately treated with either cefazolin or more clindamycin, and did not require the extended coverage of linezolid or vancomycin.

The Infectious Diseases Society of America's 2014 SSTI guidelines suggest that clindamycin is an option for mild-moderate non-purulent and severe purulent infections if the clindamycin resistance rate in the community is <10%-15%.[9] The clindamycin resistance rate at Kapi'olani Medical Center for Women and Children has been >15% for SA and up to 14% for GAS; therefore, clindamycin is not a useful single agent at this institution. Based on this institution's pediatric culture data in 2015, focusing only on SA and GAS, it was calculated that use of clindamycin alone would have been inadequate treatment for 24% of culture-positive cases (clindamycin-resistant MSSA/MRSA/GAS), cefazolin alone would have been inadequate treatment for 28% of culture-positive cases (MRSA), and the combination of cefazolin and clindamycin would have missed (been inadequate treatment for) just 9% of culture-positive cases (clindamycin-resistant MRSA). Because the majority of non-purulent, non-culturable cases are more likely to be caused by GAS and less likely by MRSA, cefazolin alone would be an acceptable alternative to the combination for these cases.[9] Based on these data, it was hypothesized that using a combination of cefazolin and clindamycin or cefazolin alone for non-purulent infections would decrease the use of linezolid and/or vancomycin.

Methods

In mid-2015, staff pediatric hospitalists and pediatric residents were educated about the potential benefits of a new antibiotic regimen consisting of a combination of intravenous cefazolin 100mg/kg/day and intravenous clindamycin 40mg/kg/day (with a dose limit of the maximum adult dose). Education consisted of presenting the local rates of antibiotic resistance, highlighting the ongoing high prevalence of MRSA and clindamycin-resistant SA and GAS, and showing that cefazolin and clindamycin duo therapy would theoretically decrease the amount of inadequately treated infections. Practitioners were also encouraged to use cefazolin alone for non-purulent infections typical of GAS. The local pediatric hospitalist SSTI practice guideline and electronic-medical record SSTI order set were updated to include the new antibiotic combination recommendation. The practice guideline was available for review as a link within the electronic medical record order set. Practitioners were still able to order vancomycin or linezolid at their discretion. Buy-in was obtained from staff pediatric infectious disease specialists after presentation of the same local antimicrobial resistance data. Practitioners were encouraged to narrow antibiotics based on culture results if available. If cultures were negative or could not be collected, the patients were sent home on cephalexin 100mg/kg/day divided 3 times per day and clindamycin 40mg/kg/day divided 3 times per day. A waiver was granted by the Hawai'i Pacific Health Institutional Review Board for this project.

A retrospective chart review was performed on patients hospitalized for uncomplicated SSTIs before the educational intervention, from May 2014 to April 2015, and after the educational intervention, from November 2015 to October 2016. Charts were pulled from the electronic medical record for patients age ≤18 with the following diagnosis codes: ICD-9 680–686, 709.9, ICD-10 L02.211-9, L02.419, L02.611-9, L03.011-9, L03.031-9, L03.111-9, L03.129, L03.211, L03.221, L03.311-9, L03.811, L03.90, L08.9. Of 483 charts reviewed manually, 205 charts were excluded based on exclusion criteria: a primary diagnosis other than SSTI; complicated SSTIs including osteomyelitis, fasciitis, septic arthritis, or bacteremia; diagnoses that may need alternative or additional antibiotic coverage other than cefazolin and clindamycin including mastoiditis, otitis externa, periorbital/orbital cellulitis, facial cellulitis of dental origin, foot infections, omphalitis, infections sustained in water, infections caused by human or animal bites.

Data were collected on age, sex, diagnosis, type, and timing of antibiotics administered, whether a switch occurred from initial antibiotic to linezolid or vancomycin, length of stay (LOS) calculated from time of first entered vital sign to time of discharge order, and wound and blood cultures. Data were analyzed using Wilcoxon rank sum for continuous variables, and Chi-squared and Fisher's Exact tests for categorical variables. Statistical analyses were performed by a statistician provided by the Hawai'i Pacific Health Summer Research Program.

Results

There were no significant differences in age, gender, or culture results between the pre-intervention and post-intervention groups. The mean age of patients was 5.6 years old (Table 1). There was no significant difference in clindamycin-resistance between groups (P=.54 and .92 for MSSA and MRSA clindamycin-resistance respectively).

There was a significant decrease in the percent of patients started on linezolid or vancomycin within the first 24 hours of admission, from 25% to 13.6% (P<.05) (Table 2). Despite fewer cases involving initial linezolid or vancomycin in the post-intervention group, there was no statistically significant change in LOS (Table 3). The raw data showed a non-statistically significant 10.5-hour difference. Secondary data review of patients with prolonged LOS >2 standard deviations (SD) from

mean revealed that some patients had prolonged LOS despite being ready for discharge from an infection standpoint. These patients were not discharged due to inability to adhere to oral antibiotics regimen, inability to perform wound care at home, or hospitalization in the neonatal intensive care unit from birth for reasons unrelated to SSTIs and for which SSTIs did not affect LOS. Recalculation of LOS without these patients showed a smaller 7-hour difference: The average pre-intervention LOS was 71.7 hours and the post-intervention LOS was 78.8 hours.

There was no significant difference between the pre- and post-intervention periods in the number of patients switched to linezolid or vancomycin (Table 2). Despite fewer patients started on linezolid or vancomycin in the post-intervention group, there was not a higher percentage of patients who were switched to linezolid or vancomycin later.

The incidence of positive blood cultures was <2% in both groups and not statistically significant between the groups (Table 4).

Table 1. Patient Demographic Data

Variable	mean ± SD (range) or n (%)			*P*-value	*P*-value using Kruskal-Wallis test
	Total (n=278)	Pre (n=160)	Post (n=118)		
Age (years)	5.6 ± 5.6 (0 - 17)	5.6 ± 5.6 (0 - 17)	5.6 ± 5.6 (0 - 17)	.97	.83
Female	131 (47.1%)	73 (45.6%)	58 (49.2%)	.64	

Table 2. Antibiotic Usage and Clindamycin Susceptibilities

Variable	Number of patients (%)			*P*-value
	Total (n=278)	Pre-intervention (n=160)	Post-intervention (n=118)	
Initial Linezolid/Vancomycin First 24hrs	56 (20.1%)	40 (25%)	16 (13.6%)	.03
Cefazolin	127 (45.7%)	25 (15.6%)	102 (86.4%)	<.0001
Clindamycin	242 (87.1%)	135 (84.4%)	107 (90.7%)	.17
Linezolid	56 (20.1%)	39 (24.4%)	17 (14.4%)	.06
Vancomycin	17 (6.1%)	6 (3.8%)	11 (9.3%)	.10
Switch to linezolid or vancomycin	48 (17.3%)	27 (16.9%)	21 (17.8%)	.97
GAS clindamycin-susceptible	67	38	29	.10
GAS clindamycin-resistant	5	4	1	.57
MSSA clindamycin-susceptible	61	42	19	.06
MSSA clindamycin-resistant	15	7	8	.54
MRSA clindamycin-susceptible	33	17	16	.58
MRSA clindamycin-resistant	11	7	4	.92

Table 3. Length of Stay

Variable	mean ± SD (range) or n (%)			*P*-value	*P*-value using Kruskal-Wallis test
	Total (n=278)	Pre-intervention (n=160)	Post-intervention (n=118)		
Length of stay (days)	79.1 ± 44.8 (14 - 294)	74.64 ± 41.35 (14 - 277)	85.1 ± 48.6 (19 - 294)	.06	.06

Table 4. Culture Data

Variable	Number of patients (%)			*P*-value
	Total (n=278)	Pre (n=160)	Post (n=118)	
Wound culture, none	88 (31.7%)	48 (30%)	40 (33.9%)	.58
Blood culture positive	4 (1.4%)	3 (1.9%)	1 (0.9%)	.84
Blood culture, none	55 (19.8%)	27 (16.9%)	21 (17.8%)	.97

Discussion

Current national guidelines recommend monotherapy for uncomplicated SSTIs, however, Kapi'olani Medical Center for Women and Children's experience with monotherapy, with high local rates of MRSA and high clindamycin-resistance of SA and GAS, had led to increased use of linezolid due to treatment failures. This project utilized 2 commonly used antibiotics, cefazolin and clindamycin, which, when used separately as monotherapy, have become ineffective due to increased local antibiotic resistance. However, the data collected in this project suggest the combination of these antibiotics has the potential to decrease use of linezolid, a broader-spectrum antibiotic, which in turn may decrease the risk for development of linezolid-resistant organisms. Decreased initiation of linezolid on admission reassuringly did not adversely affect LOS or increase the use of linezolid after the first 24 hours of hospitalization.

Limitations of this study include a small sample size and potential to affect patient compliance given the potential need to take 2 antibiotics at home in cases that do not allow for narrowing antibiotics. Dividing both cephalexin and clindamycin into 3 times per day dosing allows parents to administer both medications at the same time at flexible times, eg, "in the morning," "after school," and "before bedtime," which may help with adherence.

Clindamycin resistance in SA appears to continue to rise in other parts of the United States, but there appears to have been no significant change in clindamycin resistance in Hawai'i between 2016 and 2018.[10] It is not possible to determine at this time if this difference is due to antibiotic selection, coincidence, or other concurrent interventions such as the creation of an antimicrobial stewardship program. Future studies could include collecting larger sample sizes by analyzing longer time periods and assessing antimicrobial resistance rates on this regimen for a longer period of time.

Combination therapy with cefazolin and clindamycin is a potential option in areas of high clindamycin resistance and high MRSA prevalence and may lead to decreased need for broader MRSA coverage with linezolid.

Conflict of Interest

The authors report no conflicts of interest.

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