Mupirocin Resistance Related to Increasing Mupirocin Use in Clinical Isolates of Methicillin-Resistant Staphylococcus aureus in a Pediatric Population

Jacob S. Hogue,1,* Patricia Buttke,2 LoRanee E. Braun,1 and Mary P. Fairchok1

Department of Pediatrics, Madigan Army Medical Center, Tacoma, Washington,1 and
Penn State University College of Medicine, Hershey, Pennsylvania2

Received 30 October 2009/Returned for modification 28 December 2009/Accepted 20 April 2010

We investigated the proportion of methicillin-resistant Staphylococcus aureus (MRSA) isolates from pediatric patients demonstrating mupirocin resistance related to mupirocin use at our institution. No mupirocin resistance was found in 98% of isolates, whereas mupirocin prescriptions increased by 110%. Resistance rates remained low despite the increasing use of mupirocin.

Mupirocin is a topical antibiotic used to treat superficial skin infections and to control spread of methicillin-resistant Staphylococcus aureus (MRSA). Mupirocin resistance was described shortly after it became available (8, 11). Prevalence of mupirocin resistance among MRSA isolates has been described mostly in hospitalized adult and elderly patients with wide variability, ranging from 0 to 65% of isolates (2, 4–7, 9, 10, 12–14, 16–19). Rates of resistance have been shown to correlate with increased use in closed inpatient settings (10, 18). Rates of resistance among pediatric patients have not been as well studied, nor has there been a study evaluating the impact of increasing mupirocin use in a predominantly outpatient setting with resistance. In this study, we investigated the proportion of MRSA demonstrating mupirocin resistance among pediatric isolates in the face of increasing rates of mupirocin use at our institution.

From November 2005 to October 2007, first-time MRSA isolates obtained from pediatric patients (0 to 18 years) at a military medical center in the northwest United States were screened for mupirocin resistance. Our institution includes a large primary care pediatric clinic in addition to an inpatient pediatric ward. Most of our isolates were obtained in the outpatient setting. To evaluate mupirocin prescription trends, mupirocin prescription data were extracted from the medical center’s pharmacy database from January 2002 through December 2007. Our pharmacy database includes all prescriptions provided in both the outpatient and inpatient settings to patients served by our institution. Our institution does not have any formal guidelines limiting the prescription of mupirocin.

All isolates were categorized as MRSA using routine antibiotic susceptibility testing per the established laboratory protocol. The MRSA phenotype identified using disk diffusion on Mueller-Hinton agar was confirmed with Vitek 2 (bioMérieux) identification and susceptibility testing cards for Gram-positive bacteria. Isolates were stored at −70°C awaiting further testing. Subcultures plated on blood agar (BBL TSA) were incubated for 24 h prior to Etest and PCR. Mupirocin Etest (AB Biodisk; MIC range, 0.064 to 1,024 μg/ml) was used according to the manufacturer’s instructions on Mueller-Hinton agar. The MIC breakpoints were chosen to correlate with previous studies of mupirocin resistance (3, 9, 14, 16, 19). Mupirocin susceptibility was defined as an MIC of <8 μg/ml, intermediate resistance as an MIC of 8 to 256 μg/ml, and high-level resistance as an MIC of ≥512 μg/ml.

DNA was extracted using the Roche MagNA Pure LC system. A real-time PCR assay was performed on the LightCycler PCR platform (Roche) using custom-designed primers ordered from Sigma Genosys (The Woodlands, TX): Mup-F (5'-TAATGGG AAATGTCTCGAGTAGA-3') and Mup-R (5'-AATAAATTC AGCTGGAAGTGTG-3') primers and Mup-F probe (5' CTATGCCGTTGCTACATCAT). An IDI-MRSA assay was performed according to manufacturer’s instructions (GenOhm, San Diego, CA) using a SmartCycler II device (Cepheid, Sunnyvale, CA). Primers designed to detect mupirocin resistance were included with a SmartMix HM PCR master mix (Cepheid, Sunnyvale, CA).

The median age of the 167 patients in the study was 3 years (range, 2 days to 18 years). A total of 85 (50.9%) patients were male. The majority of the isolates, 153 (91.6%), were obtained from outpatients. Isolates were obtained from skin or soft tissue infections in 148 (88.6%) patients. Other common sites included the nares in 10 (6%) and rectum in 4 (2.4%).

Three of the isolates (1.8%; 95% CI, 0.0 to 3.8%) were highly resistant to mupirocin by Etest. None of the isolates demonstrated intermediate resistance. A total of 23 isolates underwent PCR testing for the iles-2 gene, including all of the resistant isolates. The iles-2 gene was demonstrated in all of the resistant isolates but none of the other isolates.

A total of 1,031 mupirocin prescriptions were dispensed from our institution during 2002. There was a steady and marked increase annually in the number of prescriptions, such that by 2007, there were 2,170 prescriptions filled, an increase of 110%.

Antimicrobial options for treatment of MRSA are limited, so it is critical to monitor for emergence of resistance to commonly employed agents. As far as we are aware, this is the first
study investigating the rate of mupirocin resistance among pediatric patients. We have shown that rates remained low in our population despite an approximately 2-fold increase in mupirocin prescriptions over 5 years. Our level of resistance is lower than in previous studies in which the majority of patients were adult inpatients (2, 6, 17).

The 2005 Infectious Diseases Society of America guidelines on the diagnosis and management of skin and soft tissue infections recommend mupirocin as the first line agent for impetigo in patients with a limited number of lesions while taking into account local resistance patterns (15). Mupirocin can still be considered effective therapy for impetigo in our pediatric patients given that we have demonstrated a low level of mupirocin resistance.

Eradication strategies for outpatients with recurrent MRSA skin and soft tissue infections frequently employ nasal mupirocin along with different combinations of other agents such as chlorhexidine, rifampin, and trimethoprim-sulfamethoxazole. The effectiveness of such strategies to reduce colonization and the risk of skin and soft tissue infections in pediatric outpatients is controversial. There is a wide variability in the use of such strategies among infectious disease specialists (1). A frequent concern is whether mupirocin resistance will limit its role in eradication strategies. We have provided insight into this question by showing that despite a dramatic increase in mupirocin use in our population, mupirocin resistance rates have remained low.

Our study had limitations. First, only the initial positive MRSA isolate for a patient was included in the study. Rates of mupirocin resistance could be higher with additional isolates from the same patients. Second, we did not type our isolates by mupirocin resistance. Third, we cannot exclude the possibility that patients had mupirocin resistance among specific clones (14). We have provided insight into this question by showing that despite a dramatic increase in mupirocin use in our population, mupirocin resistance rates have remained low.

We acknowledge the following individuals who provided a great deal of assistance in the completion of this study: Dana Perkins, Helen Viscoun, Haengcha Chong, Troy Patience, Chris Gibson, Mary Meyers, and David Tomich.

The opinions or assertions contained herein are our private views and are not to be construed as official or as reflecting the views of the Department of Defense.

We have adhered to the policies for protection of human subjects as prescribed in 45 CFR 46.

REFERENCES