Daptomycin Use in United States Children’s Hospitals

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We described 1035 pediatric hospitalizations with daptomycin use in 794 patients since 2004. Daptomycin use was uncommon but increased over time. A minority of hospitals accounted for the majority of use. This variability of daptomycin use highlights the need for future studies to assess the efficacy and safety of daptomycin in children.

Key words. children; daptomycin; MRSA; resistance; VRE.

INTRODUCTION

An increasing proportion of Staphylococcus aureus and Enterococcus spp. causing healthcare-associated infections display reduced susceptibility to first-line agents, including β-lactam antibiotics and vancomycin. Methicillin-resistant S. aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) infections are associated with increased mortality, morbidity, and costs across all age groups [1, 2].

Daptomycin is a lipopeptide antibiotic approved in 2003 for the treatment of complicated skin and skin-structure infections in adults. In 2006, an indication was added for S aureus bacteremia and right-sided endocarditis [3]. Daptomycin can be a useful alternative to first-line agents for infections with MRSA, methicillin-susceptible S aureus (MSSA), and VRE [4–6]. The extent of daptomycin use in pediatrics remains unclear. Therefore, we aimed to describe the use of daptomycin across freestanding children’s hospitals in the US.

METHODS

Retrospective analysis of daptomycin use in hospitalized US children during a 9-year period was conducted using the Pediatric Health Information System (PHIS) database (Children’s Hospital Association, Thomson Healthcare).

We included all patients <18 years old with at least 1 charge for daptomycin discharged between January 1, 2004 and December 31, 2012.

RESULTS

During the 9-year study period, 1035 hospitalizations with at least 1 administration of daptomycin occurred in 794 patients (<1 antibiotic-day per 1000 patient-days). Patient demographic and clinical characteristics are summarized in

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Table 1. Of note, 47.3% of children were younger than 10 years of age. MRSA was identified in 182 (17.6%) hospitalizations and Enterococcus spp. were identified in 110 (10.6%) hospitalizations.

The most frequent diagnoses and clinical categories associated with at least 1 dose of daptomycin administration are summarized in Table 1. One third of the daptomycin use occurred in hospitalizations related to oncology. The median duration of daptomycin therapy was 5 days (interquartile range [IQR] = 2–13) and the median number of daptomycin doses administered per hospitalization was 5 (IQR = 2–11). Only a single dose was administered in 161 hospitalizations (15.6%). The median duration of hospitalization for children receiving at least 1 dose of daptomycin was 19 days (IQR = 7–49). The median duration of hospitalization prior to the first dose of daptomycin was 7 days (IQR = 2–23) and the median duration of hospitalization after daptomycin therapy ended was 10 days (IQR = 3–25).

The most common antibiotics with activity against MRSA used for at least 48 hours prior to daptomycin administration were vancomycin (35.5%), linezolid (12.7%), and clindamycin (11.4%), each with a median duration of 3 days (IQR = 2–3). Linezolid (6.8%), trimethoprim/sulfamethoxazole (6.6%), and rifampin (4%) were the most common anti-MRSA antibiotics used for at least 48 hours in conjunction with daptomycin. Within 1 day after stopping daptomycin, 141 (13.6%) patients began treatment with vancomycin for at least 48 hours. Linezolid, quinupristin/dalfopristin, and tigecycline were started following daptomycin therapy in 83 (8%), 9 (0.9%), and 6 (0.6%) patients, respectively.

Daptomycin use varied across hospitals and increased steadily since 2004. More than half of all daptomycin use was accounted for by only 6 hospitals with no geographic clustering, with a single center accounting for 24% of total use. Five hospitals never administered daptomycin during the study period. A decrease in overall daptomycin use was observed in 2010, coincident with a U.S. Food and Drug Administration warning that eosinophilic pneumonia could be associated with daptomycin use [7].

Of the 1035 hospitalizations with daptomycin use, 7 children had rhabdomyolysis, 1 had pulmonary eosinophilia, and 112 (10.85%) died in the hospital (overall mortality in children <18 years at PHIS hospitals during the study period was 0.73%). Bone marrow transplant (31.3%) was the most common APR-DRG among children who died during the hospitalization.

**DISCUSSION**

Pediatric use of daptomycin was uncommon but increased steadily since its introduction in 2004. Exposure to daptomycin varied broadly across hospitals, and a small group of hospitals accounted for the majority of total daptomycin use. Daptomycin was prescribed for a wide range of conditions and almost half of daptomycin was given to children <10 years old, despite a lack of clear prescribing guidelines for this age group. This increasing and variable use of
daptomycin highlights the need for studies to assess the efficacy and safety of this agent in children.

Only 6 of 43 centers accounted for the majority of use, and a single hospital prescribed one quarter of total daptomycin doses. Possible drivers of this profound variability in daptomycin use include potential differences in the epidemiology of antibiotic resistance across centers; the distribution of medically complex patients at risk for infections with resistant pathogens; or the presence of antimicrobial stewardship programs that might limit the use of broad-spectrum agents.

Multiple reports have described daptomycin use in pediatric patients who are not responding to conventional therapies. Palma et al. reported the resolution of bacteremia and fever within 72 hours in 7 children infected with MRSA, VRE, or methicillin-resistant S. epidermidis [8]. Ardura et al. reported clinical improvement after addition of daptomycin in 14 of 16 children with severe disseminated staphylococcal diseases [9]. Case reports have shown clinical cure in young infants with substantially higher doses of daptomycin (10 mg/kg body weight) than those recommended for adults (4–6 mg/kg). In our study, 5% of daptomycin use occurred in children <1 year old [10–12]. Until the optimal pediatric dose is known, larger studies are needed to determine the effectiveness and safety of daptomycin in children.

Our study has several limitations. The data available to us did not allow identification of dosage timing of potential adverse events, or attributable cause of death. We also used APR-DRG and ICD9 codes for assigning diagnoses, which are not validated for many of the clinical entities described in this study, though are likely to be relatively specific. We could not evaluate the effectiveness of daptomycin compared with other antimicrobials or identified the specific pathogen treated.

In conclusion, pediatric daptomycin use is uncommon but increasing. The variability of daptomycin use across large tertiary children’s hospitals justifies future studies assessing the efficacy and safety of daptomycin use in children.

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