JPPT | Systematic Review

Daptomycin Experience in the Pediatric and Neonatal Population: A Systematic Review

Robyn Yarsley, PharmD; Benjamin M. Lopez, PharmD; Gabriela Alves; and Fabio Aguiar-Alves, DSci

ABBREVIATIONS AEs, adverse effects; BMT, bone marrow transplantation; CCPD, continuous cycling peritoneal dialysis; CHD, congenital heart disease; Clin, clinical; CoNS, coagulase-negative staphylococcus; CPK, creatine phosphokinase; CR, case report; CRBSI, catheter-related bloodstream infection; CS, case series; cSSTI, complicated skin and skin structure infection; CVC, central venous catheter; DAP, daptomycin; E, elevated; FDA, US Food and Drug Administration; GA, gestational age; GP, Gram positive; GPC, Gram positive cocci; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; IA, intra–abdominal; ITT, intention to treat; lab, laboratory; LZD, linezolid; micro, microbiological; mITT, modified intention to treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NR, not reported; NS, not significant; PDA, patent ductus arteriosus; PFA, patent foramen ovale; PNA, pneumonia; PP, per protocol; PS, prospective study; RA, retrospective analysis; RCT, randomized controlled trial; SOC, standard of care; SA, *Staphylococcus aureus*; SE, *Staphylococcus epidermidis*; SSI, surgical site infection; ST398, Sequence Type 398 (MRSA); ST80, Sequence Type 80 (MRSA); TEC, teicoplanin; TOC, test of cure; Tx, treatment; ULN, upper limit of normal; VAN, vancomycin; VISE, vancomycin-intermediate *Staphylococcus epidermidis*; VRE, vancomycin-resistant *Enterococcus*; VP, ventriculoperitoneal; WNL, within normal limits

KEYWORDS daptomycin; infant; neonatal; pediatric; systematic review

J Pediatr Pharmacol Ther 2025;30(4):450–463

DOI: 10.5863/JPPT-24-00056

This review examines the use of daptomycin in pediatric patients, including infants and neonates. A systematic review was conducted including articles containing safety and efficacy outcomes along with dosing information in pediatric patients receiving daptomycin. Randomized controlled trials (RCTs), prospective studies, retrospective analyses (RA), cohort studies, case reports or case series in patients less than 18 years of age were included. The review summarizes 41 articles between 2006 and 2024 (3 randomized controlled trials, 2 prospective studies, 9 retrospective reviews, and 27 case reports). Mean efficacy documented by either clinical improvement, clinical cure or microbiological cure in all prospective studies and retrospective reviews was 79.4% (range: 36.7%–100%). Dosing ranged from 4 to 12 mg/kg/day with 12 mg/kg/day administered in 2 divided doses being the most commonly used regimen in neonates and infants. There were few adverse effects reported or defined; primarily CPK elevations with no significant differences observed compared with standard of care treatments, although the quality of evidence was limited. Future prospective trials in the infant and neonatal population are warranted to determine a standard approach to treatment. This review highlights the growing body of evidence supporting the use of daptomycin in pediatrics, offering valuable insights for clinicians, particularly when faced with limited treatment options due to standard treatment failure and antimicrobial resistance.

Introduction

Daptomycin is a cyclic lipopeptide antibiotic approved in 2003 for the treatment of infections caused by Gram-positive organisms.[1] Its mechanism of action is unique compared with other antimicrobial agents. The daptomycin structure encourages the formation of complexes which interact with the negatively charged bacterial cell membrane. This leads to a conformational change in the cell membrane which causes a flow of potassium (K^+) ions out of the cell, resulting in cell death.[2] Gram-positive bacteria exhibit complex resistance, presenting challenges in health care facilities and community settings. *Staphylococcus aureus,* a common Gram-positive bacterium, can cause a range of infections from minor skin infections to severe conditions like pneumonia, bacteremia, endocarditis and osteomyelitis. Methicillin-resistant *Staphylococcus aureus* (MRSA), carries the Staphylococcal chromosomal cassette (SCC*mec*) and exhibits resistance to several classes of antimicrobial agents, significantly limiting treatment choices and emphasizing the critical need for innovative antimicrobial approaches.[3]

Guidelines endorsed by the American Academy of Pediatrics (AAP) including those from the Infectious

Disease Society of America's (IDSA) Guidelines for Treatment of MRSA in Adults and Children and the Guidelines for Management of Acute Hematogenous Osteomyelitis recommend vancomycin as a first-line agent for invasive multidrug resistant Gram-positive infections, including coagulase-negative *Staphylococcus* species (CoNS) and methicillin-resistant *Staphylococcus aureus* (MRSA), depending on infection severity, cultures and sensitivities.[4,5] In the event of vancomycin resistance, such as strains of vancomycin-resistant *Enterococcus* (VRE), adverse effects or treatment failure, alternative options include ceftaroline and linezolid, both of which have indications approved by the US Food and Drug Administration (FDA) in children.[4–6] While daptomycin is an alternative agent included in IDSA and AAP recommendations, providers may be reluctant to use it due to lack of pediatric data and differences in clearance and volume of distribution demonstrated in prior pharmacodynamic (PD) and pharmacokinetic (PK) trials in children.[7–9]

Daptomycin, originally marketed in the United States as Cubicin (Merck & Co, Inc, Rahway, NJ), is FDA-approved for complicated skin and skin structure infections (cSSTIs) and *S aureus* bacteremia in adults and pediatric patients 1 year or older. It is also approved for bloodstream infections with right-sided infective endocarditis, specifically in adults.[1] Evidence from pharmacokinetic (PK) studies in children demonstrate varying pharmacokinetics from that of adults, particularly in neonates, infants and children under 6 years of age.[9] Within the FDA-approved label, daptomycin dosing in pediatrics varies significantly from adults and is based on infection type and age. Dosing ranges from 5 mg/kg every 24 hours in adolescents with cSSTIs up to 12 mg/kg every 24 hours in children 1 to 6 years of age with *S aureus* bacteremia. Children 1 to 6 years of age should receive a 60-minute daptomycin infusion per the labelling, as opposed to the standard 30-minute infusion time in adults and older children (see Discussion). The prescribing information states it is not recommended in pediatric patients younger than 1 year of age due to risk of potential adverse effects to the muscular, neuromuscular, and nervous systems. Daptomycin is known to possibly increase blood creatinine phosphokinase (CPK) concentrations; whether this is linked to adverse events is worth investigation.[1] Several articles have reviewed pediatric daptomycin literature in the past; the most recent review by Karageorgos et al,[10] which reviewed data up until its publishing in 2016, expressed a need for additional data in infants and neonates. Since then, there has been an increase of daptomycin publications in pediatric patients. This review seeks to collect and evaluate the updated literature on the efficacy and safety of daptomycin in pediatric treatments, with a focus on children younger than 1 year of age.

Methods

Literature Review. A literature search was conducted on PubMed MEDLINE (1987–March 2024) using the search terms "daptomycin and pediatrics," "daptomycin and children," "cubicin and children," and "cubicin and pediatrics." Studies included in the review were limited to those available or translated in English and including patients from birth to 18 years of age. Articles were included if they contained patient data on receiving daptomycin, were randomized controlled trials (RCTs), retrospective analyses (RA), cohort studies, case reports or case series, and patients were less than 18 years of age. Studies performed in vitro or missing dosage information were excluded. A second search was also conducted in Clinicaltrials.gov using the search term "daptomycin," filtering for subjects 0 to 17 years and completed trials. Article bibliographies from the resulted searches were also reviewed for additional pertinent literature. Assessments of titles, abstracts, and full texts were conducted independently by 2 investigators. Authors worked independently and no automation tools were used. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to identify, screen and select articles.[11] See Supplemental Figure.

Data Extraction. Primary outcome measures of either clinical cure, clinical improvement or microbiological cure were reviewed. Clinical cure was defined based on each study or report's definition for clinical cure or improvement and was not defined universally or consistently across all studies. Laboratory markers including C-reactive protein (CRP), white blood cells (WBCs), temperature or fever monitoring, and clinical signs and symptoms of infection were all possible factors included in the reported clinical cure. Microbiological cure was defined as the absence of the original microorganism in follow-up cultures or negative cultures. Safety outcomes were also assessed based on the percentage of treatment-related adverse events reported. Laboratory markers such as creatine phosphokinase (CPK) were included if reported. Elevations in CPK due to daptomycin were defined per study. Pharmacokinetic data, dosing and infusion durations were included if provided.

Statistical Analysis. Data were collected and analyzed using descriptive statistics. For continuous variables, medians, means and ranges were reported where appropriate. Binary variables were described using frequencies and average percentages to show how common each category was reported. Missing data was not included in statistical calculations.

Results

Of the 196 articles reviewed from the MEDLINE search, 11 from bibliography searches, and 6 from clinicaltrials.gov, 172 were excluded. Duplicate articles

were removed. Reviews, susceptibility trials and animal studies were some of the most common reasons for exclusion. Other reasons for exclusion included pharmacokinetic-specific studies, studies assessing single-dose pharmacokinetics, lack of pediatric-specific data, lack of dosing information, lack of daptomycin-specific information or lack of translation available in English. Articles initially screened for inclusion may have been excluded later in the review process for multiple reasons (i.e., article did not have specific dosing information AND was not available in English). We identified a total of 41 articles (5 prospective studies, 9 retrospective analyses or case series and 27 case reports) which met inclusion for our review. Table 1 summarizes prospective studies and retrospective analyses.[12–25] Table 2 includes all case reports.[26–52] All articles included in this review were published between 2006 and March 2024.

Trials and Retrospective Reviews. Three randomized controlled trials (RCTs), 2 prospective observational studies, and nine retrospective analyses were included in the review.[12–16] The 3 RCTs compared daptomycin with standard of care (SOC) treatment, most commonly vancomycin.[12–14] As neonatal and infant studies were of particular interest, we identified 7 studies that included children under 1 year of age, 4 of which included neonates.[16–22] Age was typically reported as postnatal age (PNA), with a median age for all studies and case series of 6.5 years. Asfour et al[18] and Mohzari et al[19] were the 2 studies that reported gestational age (GA), of which the median for both studies was 27 weeks.

MRSA and MSSA were the most common organisms with bacteremia and cSSTIs as the most frequently reported types of infection. Other less frequently reported types of infection included bone and joint infections and endocarditis. Dosing ranged from 4 mg/kg/day up to 12 mg/kg/day (including 6 mg/kg/dose twice daily). Dosing varied by age, with most dosing categorized by age similar to FDA-approved prescribing information.[1] While infusion durations were infrequently reported, 4 studies specified infusions consistent with the prescribing information.[1,13–15,18] Tedeschi et al[16] reported using a 3-minute rapid infusion for the 12 patients who received daptomycin. The median duration documented was 12.5 days (range: 1–44 days). Efficacy documented by either improvement or cure across all studies and reviews varied substantially, with a mean of 79.4% (range: 36.7%–100%).

In Bradley et al[12] evaluating the safety and efficacy of daptomycin vs SOC in children with acute hematogenous osteomyelitis, power was not met due to low enrollment to detect noninferiority of clinical improvement by day 5. The RCT by Arrieta et al[13] evaluated the safety and efficacy of daptomycin vs SOC for children with Staphylococcal bacteremia with safety as the primary outcome. The article by Bradley et al[14] evaluated daptomycin compared with SOC for treatment of cSSTIs. Outcomes were reported for the intention-to-treat (ITT), modified intention-to-treat (mITT), and the clinically evaluable (CE) population.[14] Articles by Arrieta et al[13] and Bradley et al[14] were both designed with safety as the primary outcome, however these studies were not powered for efficacy or safety.

Of the RCTs reviewed, 87% of patients treated with daptomycin met clinical and/or microbiological cure in the modified intention to treat (mITT) analyses (as defined per study) with a difference in cure rates compared with SOC ranging from −7.9% to 11%. There was no statistically significant difference in efficacy found between daptomycin and the comparator groups among the 3 RCTs.[12–14] Confidence intervals of 95% were reported for primary and secondary outcomes.

Safety data were analyzed descriptively in all 3 studies.[12–14] Treatment-related adverse events were reported with an average of 28.8% with daptomycin and 37% in the SOC comparator studies (8.25% difference). In the RCT by Bradley et al[12] comparing safety of daptomycin (n = 74 patients) with SOC (n = 72 patients) in pediatric patients with osteomyelitis, patients with treatment-related adverse events occurred 6.8% in the daptomycin group vs 18.1% in the comparator group. Patients who discontinued treatment due to at least 1 adverse effect were 1.4% in the daptomycin group vs 9.7% in the SOC group. There were no serious treatment-related adverse effects in the daptomycin group, while 4.2% of the comparator group experienced serious adverse effects such as pyrexia, drug reaction with eosinophilia and systemic symptoms (DRESS) and red man syndrome.[12] Arrieta et al[13] reported an increase in blood CPK concentrations above the normal range (reported as 39 to 308 U/L) in 7.3% of patients receiving daptomycin (n = 55) vs no increase in CPK concentrations in the SOC (n = 27) group (values ranged from 19 to 545 U/L) however, it was deemed that only 2 cases (3.6%) were attributed to daptomycin therapy. Bradley et al[14] reported increased serum CPK concentrations in 14 (5.5% of daptomycin patients) and 7 (5.3% of the SOC patients). Only 1 case of elevated serum CPK concentration was deemed to be related to daptomycin. In Bradley et al[12] increases in CPK blood concentrations following treatment were reported in 7 (11%) daptomycin patients and 4 (6%) SOC patients, however all were less than or equal to 2.5 times the upper limit of normal and resolved during or following treatment.

In summary of all prospective and retrospective studies, treatment-related or possible adverse effects were reported in 13 of the 14 articles. Adverse effects occurred in an average of 10.2% (range: 0%–65.5%) of patients. Whereas 7 of the 8 studies that included infants (n = 7) and/or neonates (n = 4) reported an average of 4.2% of treatment-related adverse events (range: 0%–11.1%). A significant increase in CPK concentrations as defined per study, was reported an average

Table 1. Daptomycin Pediatric Prospective and Retrospective Studies

First Author	Study Design (Comparator)	DAP Patients, n (Total Patients)	Median Age (IQR)	Population	Infection Type	Organism	DAP Dose (by age)	Tx Duration*, Days (range)	Measure of Treatment Success	% Patients Successful Treatment (Outcome Difference, 95% CI)	Tx-Related AEs†	Elevated CPK
RCTs												
Bradley[12]	RCT (SOC) mITT	74 (149)	9.75 yr (1.2–17.3)	Children	Bone/joint	GP	7 mg/kg/day (12–17 yr) 9 mg/kg/day (7–11 yr) 12 mg/kg/day (1–6 yr)	8 (1–42)	Clin improvement by day 5, Clin cure at end of Tx	77.5% vs 82.9% SOC (–6.1%, –19.4 to 7.4) 83.1% vs 89.9% SOC (–7.9, –19.8 to 4)	6.8% vs 18.1% SOC	4%
Arrieta[13]	RCT (SOC) mITT	55 (81)	9.6 yr (2–16.9)	Children	Bacteremia, cSSTI, IA, Bone/joint	MRSA, CoNS, MSSA	7 mg/kg/day (12–17 yr) 9 mg/kg/day (7–11 yr) 12 mg/kg/day (1–6 yr)	11 (1–44)	Clin and micro resolution	88% vs 77% SOC (11%, –9 to 31%)	65.5% vs 76.9% SOC	7.3% vs 0% SOC
Bradley[14]	RCT (SOC) mITT	257 (389)	NR	Children	cSSTI	GP (35% MRSA)	5 mg/kg/day (12–17 yr) 7 mg/kg/day (7–11 yr) 9 mg/kg/day (2–6 yr) 10 mg/kg/day (12–23 mo)	NR (1–10)	Clin improvement	90.9% vs 86.7% SOC (4.2%, –3.3 to 11.8)	14% vs 17% SOC	5.5% vs 5.3% SOC
Prospective studies												
Iwata[15]	PS	18	7 yr (1–15 yr)	Children	cSSTI, Bacteremia	GP	10mg/kg/day (1 to < 2 yr) 9 mg/kg/day (2–6 yr) 7 mg/kg/day (7–11 yr) 5 mg/kg/day (12–17 yr)	6 (5–14)	Clin and micro resolution	83.30%	11.1%	0%

(*Table cont. on page 454*)

Table 1. Daptomycin Pediatric Prospective and Retrospective Studies *(cont.)*

First Author	Study Design (Comparator)	DAP Patients, n (Total Patients)	Median Age (IQR)	Population	Infection Type	Organism	DAP Dose (by age)	Tx Duration*, Days (range)	Measure of Treatment Success	% Patients Successful Treatment (Outcome Difference, 95% CI)	Tx-Related AEs†	Elevated CPK
Tedeschi[16]	PS	12	192 days (14 days–7 yr)	Neonates, infants	Bacteremia, cSSTI	CoNS	8 mg/kg/day	14	Micro resolution	100%	0	0%
Retrospective studies												
Vonasek[17]	RA	147	3 yr (0.75–8 yr)	Infants, children	Bacteremia, SSTI, SSI, IA, empiric, others	CoNS, *Enterococci,* MRSA, MSSA, others	4–12 mg/kg/day in divided doses	8.5, median (IQR 6–15)	Clin improvement	36.7%	1.4%	2%
Asfour[18]	CS	10	39 days (14–62 days)	Neonates, preterm infants	CoNS Bacteremia	CoNS	6 mg/kg every 12 hr or 10 mg/kg/day	24 (1–44)	Clin and micro resolution	50%	0	0
Mohzari[19]	RA	21	5 days (2–26 days)	Neonates, preterm infants	Endocarditis, sepsis, bacteremia	CoNS	6 mg/kg/dose BID (n = 8) or 10 mg/kg/day (n = 8)	22 (4–43)	Clin improvement	61.90%	9.5%	0
Rosanova[20]	RA	28	45.5 mo (12–117 mo)	Infants	Endocarditis, sepsis, bacteremia, others	GP	10 mg/kg/day (Range: 6–12 mg/kg/day)	19 (IQR 7–42)	Clin and micro resolution	78.50%	11%	7%
Namtu[21]	RA	109	12 yr (2.5 mo –24 yr)	Infants, children	CRBSI, bacteremia, cSSTI, Bone/joint	CoNS, *Enterococci* MSSA, MRSA, *Bacillus sp,* others	Children's Hospital dosing protocol: 10 mg/kg/day (≤ 6 yr) 8 mg/kg/day (> 6 to < 12 yr) 6 mg/kg/day (≥ 12 yr)	16 (3–121) 12, median	Clin or lab evidence of resolution	98%	NR	4%

(*Table cont. on page 455*)

Table 1. Daptomycin Pediatric Prospective and Retrospective Studies *(cont.)*

First Author	Study Design (Comparator)	DAP Patients, n (Total Patients)	Median Age (IQR)	Population	Infection Type	Organism	DAP Dose (by age)	Tx Duration*, Days (range)	Measure of Treatment Success	% Patients Successful Treatment (Outcome Difference, 95% CI)	Tx-Related AEs†	Elevated CPK
Syrogiannopoulos[22]	RA	128	2.8 (8 days–14 yr)	Neonates, infants	cSSTI	SA	10 mg/kg/day	10 (IQR 7–14)	Clin and micro resolution	96.1%	0	7%
Garazzino[23]	RA	46	8.7 (2.6–14.5 yr)	Children	CVC–related sepsis, osteomyelitis, cSSTI, endocarditis	MRSA, CoNS MSSA, *Enterococci*	6 mg/kg/day (6–8 IQR)	14 (IQR 10–26.5)	Clin improvement	70.4%	6.5%	0
Syriopoulou[24]	RA	81	13 (8–16 yr)	Infants, Children	Bone/joint, cSSTI, bacteremia, endocarditis, others	GP: MRSA, MSSA, CoNS, *Enterococci*	6 mg/kg/day (4–10 mg/kg/day)	12.5 (IQR 7–25)	Clin and micro resolution	92.5%	7.4%	1.2%
Ardura[25]	RA	16	6.5 yr	NR	Bacteremia, cSSTI, others	MRSA, MSSA, VRE	4–6 mg/kg/day	10 (6–34)	Micro resolution	88%	0	0

AE, adverse effects; CCPD, continuous cycling peritoneal dialysis; Clin, Clinical; CoNS, coagulase–negative Staphylococcus; CPK, creatine phosphokinase; CR, case report; CRBSI, catheter–related bloodstream infection; CS, case series; cSSTI, complicated skin and skin structure infection; CVC, central venous catheter; GP, Gram positive; GPC, Gram positive cocci; IA, intra–abdominal; ITT, intention to treat; Micro, microbiological; mITT, modified intention to treat; MRSA, methicillin–resistant Staphylococcus aureus; MSSA, methicillin–sensitive Staphylococcus aureus; NR, not reported; PP, per protocol; PS, prospective study; RA, retrospective analysis; RCT, randomized controlled trial; SA, Staphylococcus aureus; SE, Staphylococcus epidermidis; SSI, surgical site infection; ST398, Sequence Type 398 (MRSA); TOC, test of cure; Tx, treatment; ULN, upper limit of normal; VAN, vancomycin; VRE, vancomycin–resistant Enterococcus

* Mean values used unless otherwise specified.

† AEs during Tx include neurologic or nerve conduction abnormalities, musculoskeletal (weakness, myalgia), CPK elevations, rise in SCr not correlated with other causes, elevated other markers.

Table 2. Daptomycin Pediatric and Neonatal Case Reports

First Author	Age at Tx	PMH	Infection Type	Organism (Resistance)	DAP dose (mg/kg/day)	Tx Duration (days)	Measure of Improvement	Time to Improvement (days)	Reason for switch to DAP	AE[¶]	CPK	Clin Cure (Y/N)
Infant and neonatal reports												
Heger[26]	13 days	Premature, 30-wk GA	CRBSI Bacteremia	MRSA	12* 6 mg/kg every 12 hr	59	Negative culture	6	Less invasive monitoring	Y	E‡	Y
Kang[27]	6 mo	Heart-lung transplant	Bacteremia, cSSTI	VRE	10	14	Negative culture	2	C&S showing resistance	NR	NR	Y
Minotti[28]	34 days	Premature, 24-wk 5-day GA	Endocarditis	CoNS VISE	12* 6 mg/kg every 12 hr	NR	Negative Culture, CRP	3	Clin & micro failure	Y#	WNL	Y
Shigeta[29]	36 days	Premature, 23-wk GA, PDA, PFO	Endocarditis	CoNS	7.8	58	Negative Culture	2	Micro failure	N	WNL	Y
Chan[30]	15 days	Premature, 28- wk 1-day GA	Endocarditis	MRSA	12* 6 mg/kg every 12 hr	40	Clinical/ lab	18	Micro failure	N	WNL	Y
Sahin[31]	2.5 mo	Meningomyelocele hydrocephalus	Meningitis	VRE	8	15	Lab, negative culture	5	Clin & micro failure	N	WNL	Y
Sanchez[32]	8 mo	NS	Pericarditis, cSSTI	MRSA	6	5	Clinical/lab	NR	Clin failure; VAN not therapeutic	NR	NR	Y
Gawronski[33]	25 days	Premature, 24-wk 1 day GA, renal impairment	Bacteremia	MRSE	12* 6 mg/kg every 12 hr	15	Negative culture	1	Micro failure, therapeutic VAN Tx	N	WNL	Y
Tsironi[34]	28 days	NS	SSTI	MRSA (PVL+ ST80)	12	42	Clinical/lab	10	Initial Tx	N	WNL	Y
Hussain[35]	23 days	Premature, 27-wk 4 day, PDA	Bacteremia	MRSA (VISA)	10 15† Infused over 40 min	14	NR	NR	C&S data showing resistance	N	WNL	Y
Porter[36]	106 days	Premature, 25-wk GA, NEC, VP shunt	CNS	CoNS (VRSE)	6	28	Negative culture	3	Micro failure, developed VAN resistance	NR	NR	Y

(*Table cont. on page 457*)

Table 2. Daptomycin Pediatric and Neonatal Case Reports *(cont.)*

First Author	Age at Tx	PMH	Infection Type	Organism (Resistance)	DAP dose (mg/kg/day)	Tx Duration (days)	Measure of Improvement	Time to Improvement (days)	Reason for switch to DAP	AE[¶]	CPK	Clin Cure (Y/N)
Sarafidis[37]	38 days	Premature, 27-wk 3 day GA RDS	Bacteremia	CoNS *E. faecium* (day 23)	12* 6 mg/kg every 12 hr	17	Negative culture, clinical	2	Micro failure	N	WNL	Y
Beneri[38]	2 mo	Full term, CHD	Bacteremia	VRE	6[†]	56	Negative culture	7*	Micro failure	N	WNL	Y
Child and adolescent reports												
Kinoshita[39]	13 yr	NS	UTI	CoNS (Mec A)	6.5	13	Clinical/lab	NR	AE to prior Tx	N	WNL	Y
Yozgat[40]	16 yr	NS	Endocarditis	MSSA	8	3	Negative culture, clinical	5	NR	N	WNL	Y
Hall[41]	12 yr	NS	Bacteremia, cSSTI	MRSA	10	42	Negative culture, clinical/ lab	8	Clin & micro failure	NR	NR	Y
Morris[42]	8 yr	CHD	Bacteremia	MRSE	8 mg/kg every 48 hr	19	Negative culture, clinical/ lab	2	Potentially resistant to VAN/TEC	N	WNL	Y
Buyukcam[43]	3 yr	AML, Down syndrome	CRBSI Bacteremia	VRE	8	35	NR	NR	Clin & micro failure	N	WNL	Y
Prabhudesai[44]	3.5 yr	Renal failure, coagulopathy	Endocarditis + CRBSI	MRSA	12	56	Negative culture, clinical/ lab	3	Clin & micro failure	N	WNL	Y
Billups[45]	8 yr	Recurrent MRSA SSTI	Bone/joint	MRSA	8	35	Clinical/lab	1	Clin failure	N	WNL	Y
Jalal[46]	12 yr	CHD	Bacteremia, endocarditis	MRSA	10	28	Negative culture, clinical/ lab	3	C&S data showing resistance	N	WNL	Y
Mutschler[47]	10 yr	Trauma/ hemipelvectomy	Bacteremia, cSSTI	VRE (van-b) (LZD-resistant)	8	17	NR	NR	Micro failure (LZD resistant)	NR	NR	Y
Erturan[48]	16 yr	NS	Bacteremia, osteomyelitis,	MRSA - PVL+ST80	8	21	Negative culture, clinical/ lab	10	Clin failure	NR	NR	Y

(*Table cont. on page 458*)

Table 2. Daptomycin Pediatric and Neonatal Case Reports *(cont.)*

First Author	Age at Tx	PMH	Infection Type	Organism (Resistance)	DAP dose (mg/kg/day)	Tx Duration (days)	Measure of Improvement	Time to Improvement (days)	Reason for switch to DAP	AE[¶]	CPK	Clin Cure (Y/N)
Fossati[49]	11 yr	Post-HSCT	Bacteremia	VRE VanA PCR Positive	4	9	Negative culture, clinical/ lab	N	C&S data showing resistance	NR	NR	N
Jaspan[50]	21 mo	Leukemia	Bacteremia, Meningitis	VRE (CC17, LZD-resistant)	4 mg/kg every 12 h[§]	56	Negative culture	14	Clin & micro failure	NR	NR	Y
Jacobson[51]	15 yr	Burns	CRBSI Bacteremia	MRSA	6	7	Negative culture, clinical	N	AE to prior Tx	NR	NR	N
Akins[52]	13 yr	GVHD, aplastic anemia, BMT	Endocarditis	VRE	8	8	Negative culture	NR	C&S data showing resistance	N	WNL	Y

AEs, adverse effects; BMT, bone marrow transplantation; CCPD, continuous cycling peritoneal dialysis; CHD, congenital heart disease; Clin, clinical; CoNS, coagulase-negative Staphylococcus; CPK, creatine phosphokinase; CR, case report; CRBSI, catheter-related bloodstream infection; CS, case series; cSSTI, complicated skin and skin structure infection; CVC, central venous catheter; DAP, daptomycin; E, elevated; GA, gestational age; GP, Gram positive; GPC, Gram positive cocci; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; ITT, intention to treat; lab, laboratory; LZD, linezolid; Micro, microbiological; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; MRSE, methicillin-resistant Staphylococcus epidermidis; NR, not reported; NS, not significant; PDA, patent ductus arteriosus; PFA, patent foramen ovale; PNA, pneumonia; PP, per protocol; SA, Staphylococcus aureus; SE, Staphylococcus epidermidis; ST398, Sequence Type 398 (MRSA); ST80, Sequence Type 80 (MRSA); TEC, teicoplanin; TOC, test of cure; Tx, treatment; VAN, vancomycin; VISE, vancomycin-intermediate Staphylococcus epidermidis; VRE, vancomycin-resistant Enterococcus; VP, ventriculoperitoneal; WNL, within normal limits; Y, yes

* Daily dose was divided q 12 hr.
† Dose was adjusted during treatment course.
‡ CPK became elevated on Tx day 45 to 70 units/L, then 304 units/L on Tx day 67.
§ Daptomycin was concomitantly administered intraventricularly as 2.5 mg in 5 mL normal saline via the ventriculostomy tube daily and locked for 30 minutes, then opened for CSF drainage.
¶ AEs during Tx include neurologic or nerve conduction abnormalities, musculoskeletal (weakness, myalgia), CPK elevations, rise in serum creatinine not correlated with other causes, elevated other markers.
# Daptomycin was discontinued after patient developed eosinophilic pneumonia while on treatment. Pneumonia and infection resolved.

of 2.8%. Significant increases in CPK varied per study from greater than 1 to greater than 2.5 times the upper limit of normal (ULN) from baseline during daptomycin therapy. A rise in CPK was not confirmed to be caused by daptomycin in any of the patients.[12–25]

Case Reports. Twenty-seven case reports (Table 2) were identified for this review.[26–33,36–52] Of the 27 published case reports, 13 (48%) were of children under 1 year of age. The median age reported was 1.73 years (range 13 days–16 years). If GA was reported, it was included within Table 2. The most common organisms identified were MRSA (n = 11), VRE (n = 8) and CoNS (n = 7), specifically *S epidermidis* (n = 5) and the most treated infections were bacteremia (n = 16), endocarditis (n = 7), and cSSTIs (n = 5). Median daptomycin dosing used was 10 mg/kg/day (range: 4–15 mg/kg/day). In the subset of children less than 1 year of age, the most common dose of daptomycin was 12 mg/kg/day, typically divided into 6 mg/kg IV every 12 hours (n = 5). Infusion durations were only reported in 1 case report of a neonate who received up to 15 mg/kg as a 40-minute intravenous infusion.[35] The median duration of daptomycin therapy was 21 days (range: 3–59 days). Time to clinical improvement was noted to be an average of 6.2 days (1–18 days) with a median of 4 days and clinical cure was reported in 25 of the 27 case reports (92.5%).

Safety was reported in 18 of the 27 case reports.[26,28–31,33–36,38–41,43–46,52] Of the 18 reports, 1 patient developed eosinophilia and daptomycin was discontinued, although the cause of the eosinophilia was not determined.[28] One patient started with a baseline CPK of 29 U/L measured on day of life 25 (DAP treatment day 12) which increased to 405 U/L on day of life 53 (DAP treatment day 40 and LZD treatment day 8).[26] Daptomycin was not discontinued in this case and continued through day 72. The last follow-up CPK concentration was 308 on day 67 of therapy with no mention of adverse effects. The remaining 17 case reports reported CPK concentrations within normal limits.

The most common prior antibiotics used were vancomycin (n = 20) and linezolid (n = 8). The majority (n = 17) of patients had overlap of antibiotics during daptomycin treatment with linezolid (n = 6), rifampin (n = 5), and gentamicin (n = 4) overlapping most frequently. Most frequently reported reasons for switch to daptomycin included clinical and microbiological failure on prior treatment (n = 6), microbiological failure (n = 7), and documented culture and sensitivity data showing resistance (n = 5). Antimicrobial resistance data was infrequently reported. PVL-positive ST80 MRSA phenotypic resistance was reported in 2 cases.[35,48] Of the VRE strains, CC17-ST412 clonal complex was reported in 1 case report.[50] Susceptibilities to daptomycin were reported in 19 of the 27 case reports with a median MIC of 1 mcg/mL (range: 0.064–2 mcg/mL) across a range of Gram-positive bacteria.[26,28,30,31,33–35,37–39,41–44,46,49–52] Pharmacokinetic data were infrequently reported and, therefore, not included within Table 2. Three case reports (aged 15 days, 28 days and roughly 2 months of age) reported daptomycin serum peak concentrations using a dosing strategy of 6 mg/kg every 12 hours ranging from 27.26 mcg/mL to 51.9 mcg/mL.[30,34,38]

Discussion

Daptomycin Treatment Success and Rational for Daptomycin Use. Since the most recent review in pediatrics, 3 RCTs have been added to the literature on the use of daptomycin in pediatrics.[10] There has also been an increase in studies, case reports, including use in neonates and infants. Of the 3 RCTs published, clinical success of daptomycin was reported as an average of 85.5%, with an overall success of 79.4% within the retrospective analyses, prospective studies and RCTs combined. As the RCTs did not meet power for efficacy nor were they designed to prove efficacy, noninferiority or superiority as the primary outcome, no inferences on the results compared with SOC can be made. Pooled data indicate that daptomycin achieved clinical success in most patients. Among the RCTs there was no significant difference in defining clinical success, clinical cure, or test-of-cure.

In summary of the case reports, clinical cure was achieved in 92.5% of the reports. Case reports indicated switches to daptomycin due to clinical or microbiological failure, adverse event to prior treatment, less invasive monitoring, and subtherapeutic vancomycin troughs. These factors emphasize daptomycin's role in therapy, particularly once first-line agents fail or with documented or suspected antimicrobial resistance. Active surveillance for increasing vancomycin resistance patterns such as those associated with sequence type (ST) 80 MRSA and clonal complex (CC) 17-ST412 VRE can be used to support an early switch to daptomycin to prevent treatment failure.[55] There was no significant difference in defining clinical success or clinical cure between the case reports.

Dosing and Pharmacokinetic Considerations. This review also aimed to explore dosing strategies used in neonates and infants. For infants and neonates, the most common dose of daptomycin was 6 mg/kg IV every 12 hours (12 mg/kg/day). Within the case report by Gawronski et al[33] dosing and pharmacokinetic parameters for several case reports were summarized. In preterm neonates with normal renal function between 27 and 80 days post-natal age, daptomycin 6 mg/kg/dose every 12 hours yielded peaks ranging from 22.9 to 41.7 mg/dL, compared with older full-term neonates which yielded lower peaks ranging from 10.9 to 17.7 mg/dL, yet similar troughs as preterm neonates.[23] This suggests a highly variable and inverse relationship with distribution and clearance in preterm neonates vs term infants in line with what was also summarized in a previous review article reporting on

pharmacokinetics of 11 studies, including infants and neonates.[10] In the case of a full-term infant, pharmacokinetic monitoring was used to adjust daptomycin dosing from 4 mg/kg to 6 mg/kg every 36 hours based on a low daptomycin serum peak (6.19 mcg/mL). Following dosage adjustment, blood cultures became negative.[39] Doses as high as 15 mg/kg daily over 40 minutes in a 23-day-old neonate were reported with pharmacokinetic and safety monitoring and no reported adverse effects.[35]

Concentration-dependent nerve toxicity was observed in preclinical trials in juvenile dogs, providing rationale for using prolonged infusion times for young children in clinical trials, and the basis for the infusion recommendations in the daptomycin prescribing information. Nerve toxicity was observed at significantly lower daptomycin peak concentrations in juvenile dogs compared with adults and therefore, longer infusion times were used in children up to 6 years of age in pediatric studies to theoretically reduce peak concentrations while not affecting the overall AUC.[1,8,56] In the prospective observational study by Tedeschi et al,[16] a 3-minute daptomycin rapid infusion of 8 mg/kg was administered to 12 patients with no adverse effects. This is the only study that reported an infusion duration in neonates and infants although it is unclear how many patients were less than 1 year of age.[16] In a phase 1 single-dose pharmacokinetic safety study by Bradley et al,[56] daptomycin was administered over 30 minutes at 4 mg/kg in patients 3 to 12 months and 6 mg/kg in patients 13 to 24 months with no significant adverse effects. Given limited reports in the literature and no published studies directly comparing daptomycin infusion durations with adverse effects in pediatric patients, clinicians should consider daptomycin pharmacokinetics, weighing the risks and benefits of a shorter infusion until more evidence is available.

Safdar et al[53] reported in previous PK/PD analysis that peak to MIC and 24-hour AUC to MIC ratios best correlated with daptomycin efficacy. Mean daptomycin AUC to MIC ratios reported for 1-log killing were 666 for *Staphylococcus aureus* and 4.14 to 33.8 for *E faecium*. Mean peak to MIC ratios reported for 1-log bactericidal activity against *S aureus* were 129 +/− 24.1 with a range of 86 to 184 and 0.62 to 5.05 for tested *E faecium* isolates.[53] Based on Monte Carlo PK simulations conducted in a study by Wei et al,[54] higher dosing of 8 to 12 mg/kg in infants and children, specifically 12 mg/kg/day in infants 3 to 12 months was affirmed as being necessary to achieve probable responses to infections caused by *S aureus* and *E faecium*. Achieving desired peak to MIC and AUC to MIC concentrations with higher doses is something to consider in overcoming treatment failure due to suboptimal pharmacokinetics and dosing.

Daptomycin Treatment Success and Rational for Daptomycin Use. Of the 3 RCTs published, clinical success of daptomycin was reported as an average of 87%, with an overall success of 78% within the retrospective analyses and RCTs combined. As the RCTs did not meet power for efficacy nor were they designed to prove efficacy noninferiority or superiority as the primary outcome, no inferences on the results compared to SOC can be made. Pooled data indicate that daptomycin achieved clinical success in most patients.

Of the case reports, clinical cure was achieved in 92.5% of the reports. Case reports indicated switches to daptomycin due to clinical or microbiological failure, adverse event to prior treatment, less invasive monitoring, and subtherapeutic vancomycin trough concentrations. These factors emphasize daptomycin's role in therapy, particularly once first-line agents fail or exhibit resistance. Active surveillance for increasing vancomycin resistance patterns such as those associated with sequence type (ST) 80 MRSA and clonal complex (CC) 17-ST412 VRE can be used to support an early switch to daptomycin to prevent treatment failure.[55]

Genotyping and Resistance. This review highlights 2 significant MRSA cases with documented resistance.[34,48] The first, by Erturan et al,[48] was associated with osteomyelitis, while the second by Tsironi et al,[34] was an ophthalmic infection. Both infections were caused by Panton-Valentine Leucocidin (PVL) positive strains belonging to the ST80 lineage.[34,48] These cases demonstrated clinical success after treatment with daptomycin compared to the standard anti-MRSA regimen. This suggests that daptomycin may be a promising treatment option for MRSA infections, especially those caused by PVL-positive ST80 strains. Overall, these findings underscore the importance of considering alternative treatments such as daptomycin for managing MRSA infections, particularly when dealing with strains that exhibit unique genotypic characteristics like PVL positivity and specific clonal types.

Adverse Effects. Of the 3 RCTs included in the review, treatment-related adverse events occurred 8.3% less often than with SOC, although we cannot confirm statistical significance due to lack of power and statistical reporting. Only 1 case report cited substantially elevated CPK concentrations during daptomycin therapy. Elevated CPK concentrations reported in the daptomycin prescribing information were based on Bradley et al,[14] studying daptomycin for cSSTIs in children. CPK was elevated in 5.5% of patients in the daptomycin group vs 5.3% in the comparator group.[1,14] Bradley et al[12] found no serious treatment-related adverse effects in pediatric patients with osteomyelitis treated with daptomycin. Eight of the studies included in this review were conducted in infants or neonates, showing not only use of daptomycin in this population, but a low percentage of adverse effects (4.2%). Significant CPK elevations were only reported an average of 2.8% across all studies and retrospective analysis. Among the 27 pediatric case reports using

daptomycin, only 2 noted adverse effects, with more than half (63%) of cases monitoring and confirming normal CPK concentrations.[26,28] In a population with limited high-quality evidence, the currently summarized observations in this review demonstrate use with little to no reported toxicity compared to what is reported in the product labelling.[1]

Limitations

This review is limited by publication bias, as treatment failures may have not been published. There is limited high-quality evidence, only 3 RCTs, none of which met power for outcomes. Significant heterogeneity amongst studies and reports exists. There is also variance in definitions of clinical success, clinical cure, and treatment-related adverse effects.

Conclusions

Daptomycin may be a promising alternative for treating Gram-positive infections in pediatric patients, including neonates and infants, when other antibiotics are deemed ineffective or inappropriate. Higher dosing was used in infants and children with limited reported adverse effects. Future prospective trials in the infant and neonatal population are warranted to determine a standard approach to treatment. Exploring daptomycin efficacy compared to SOC in specific resistance patterns is another area of interest. This review provides use of daptomycin in the pediatric population over the last 15 to 20 years, specifically highlighting a significant increase in articles published after the last systematic review and those in infants and neonates. It offers valuable insights for clinicians considering daptomycin therapy in pediatric patients, particularly when faced with limited treatment options due to antimicrobial resistance or potential concern of increased adverse effects when needing to utilize higher dosing strategies in younger patients.

Article Information

Affiliations. Department of Pharmacy Practice (RLY), Palm Beach Atlantic University, Lloyd L. Gregory School of Pharmacy, West Palm Beach, FL; Department of Pharmacy (BL), HCA Florida Palms West Hospital, Loxahatchee, FL; Department of Pharmaceutical Sciences (GA, FAA), Palm Beach Atlantic University, Lloyd L. Gregory School of Pharmacy, West Palm Beach, FL.

Correspondence. Robyn Yarsley, PharmD, BCPS; robyn_yarsley@pba.edu

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the review and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors attest to meeting the 4 criteria recommended by the ICMJE for authorship of this manuscript.

Ethical Approval and Informed Consent. Institution review board/ethics committee review was not required due to the type of article.

Acknowledgments. RLY, BL, and FAA contributed to the concept and design of the review. RLY and BL performed a literature search and screened all papers. RLY, BL, GA, and FAA extracted data for the review. Data management and interpretation was conducted by RLY and validated by BL and FAA. All authors listed have contributed significantly to the work through substantial contributions such as drafting and revising the manuscript. All people named in the Acknowledgments section have agreed to their inclusion in the manuscript. The final version of the manuscript was approved by all authors.

Submitted. June 8, 2024

Accepted. October 2, 2024

Supplemental Material. DOI: 10.5863/JPPT-24-00056.S1

References

1. Cubicin [package insert]. Rahway, NJ: Merck & Co.; Inc. January 2022. Accessed May 22, 2024. https://www.merck.com/product/usa/pi_circulars/c/cubicin/cubicin_pi.pdf
2. Straus SK, Hancock RE. Mode of action of the new antibiotic for Gram-positive pathogens daptomycin: comparison with cationic antimicrobial peptides and lipopeptides. *Biochim Biophys Acta*. 2006;1758(9):1215–1223.
3. Vanamala K, Tatiparti K, Bhise K, et al. Novel approaches for the treatment of methicillin-resistant Staphylococcus aureus: using nanoparticles to overcome multidrug resistance. *Drug Discov Today*. 2021;26(1):31–43.
4. Liu C, Bayer A, Cosgrove SE, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–e55.
5. Woods CR, Bradley JS, Chatterjee A, et al. Clinical Practice Guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics. *J Pediatric Infect Dis Soc*. 2021;10(8):801–844.
6. Teflaro (ceftaroline fosamil) for injection [package insert]. Madison, NJ: Allergan USA Inc; December 2021. Accessed May 22, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/200327s028lbl.pdf
7. Calov S, Munzel F, Roehr AC, et al. Daptomycin pharmacokinetics in blood and wound fluid in critical ill patients with left ventricle assist devices. *Antibiotics (Basel)*. 2023;12(5):904.
8. Abdel-Rahman SM, Chandorkar G, Akins RL, et al. Single-dose pharmacokinetics and tolerability of daptomycin 8 to 10 mg/kg in children aged 2 to 6 years with suspected or proved Gram-positive infections. *Pediatr Infect Dis J*. 2011;30(8):712–714.

9. Abdel-Rahman SM, Benziger DP, Jacobs RF, et al. Single-dose pharmacokinetics of daptomycin in children with suspected or proved gram-positive infections. *Pediatr Infect Dis J*. 2008;27(4):330–334.
10. Karageorgos SA, Miligkos M, Dakoutrou M, Tsioutis C. Clinical effectiveness, safety profile, and pharmacokinetics of daptomycin in pediatric patients: a systematic review. *J Pediatric Infect Dis Soc*. 2016;5(4):446–457.
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
12. Bradley JS, Arrieta AC, Digtyar VA, et al. Daptomycin for pediatric Gram-positive acute hematogenous osteomyelitis. *Pediatr Infect Dis J*. 2020;39(9):814–823.
13. Arrieta AC, Bradley JS, Popejoy MW, et al. Randomized multicenter study comparing safety and efficacy of daptomycin versus standard-of-care in pediatric patients with staphylococcal bacteremia. *Pediatr Infect Dis J*. 2018;37(9):893–900.
14. Bradley J, Glasser C, Patino H, et al. Daptomycin for complicated skin infections: a randomized trial. *Pediatrics*. 2017;139(3):e20162477.
15. Iwata S, Koyama H, Murata Y. Efficacy and safety of daptomycin in Japanese pediatric participants with complicated skin and soft tissue infections or bacteremia caused by gram-positive cocci. *J Infect Chemother*. 2022;28(3):406–412.
16. Tedeschi S, Tumietto F, Conti M, et al; S. Orsola Antimicrobial Stewardship Team. Use of daptomycin in critically ill children with bloodstream infections and complicated skin and soft-tissue infections. *Pediatr Infect Dis J*. 2016;35(2):180–182.
17. Vonasek BJ, Samuel AM, Henderson SL, et al. Safety and treatment outcomes of infants and children treated with daptomycin: six-year experience from a pediatric academic medical center. *Clin Pediatr (Phila)*. 2025;64(1):18–24.
18. Asfour SS, Asfour RS, Khalil TM, Al-Mouqdad MM. The use of daptomycin in the treatment of persistent coagulase-negative staphylococcal sepsis in premature infants: a case series. *J Pediatr Pharmacol Ther*. 2021;26(1):92–98.
19. Mohzari Y, Aljobair F, Alrashed A, et al. Safety and efficacy of daptomycin in neonates with coagulase-negative staphylococci: case series analysis. *Antibiotics (Basel)*. 2021;10(2):168.
20. Rosanova MT, Sberna N, Sarkis C, et al. Experience with daptomycin in a tertiary pediatric hospital]. *Rev Chilena Infectol*. 2020;37(1):19–22. Experiencia con el uso de daptomicina en un hospital pediatrico de alta complejidad.
21. Namtu KC, Crain JC, Messina AF, et al. Clinical experience with daptomycin in pediatrics. *Pharmacotherapy*. 2017;37(1):105–108.
22. Syrogiannopoulos GA, Michoula AN, Petinaki E, Grivea IN. Daptomycin use in children: experience with various types of infection and age groups. *Pediatr Infect Dis J*. 2017;36(10):962–966.
23. Garazzino S, Castagnola E, Di Gangi M, et al. Daptomycin for children in clinical practice experience. *Pediatr Infect Dis J*. 2016;35(6):639–641.
24. Syriopoulou V, Dailiana Z, Dmitriy N, et al. Clinical experience with daptomycin for the treatment of Gram-positive infections in children and adolescents. *Pediatr Infect Dis J*. 2016;35(5):511–516.
25. Ardura MI, Mejias A, Katz KS, et al. Daptomycin therapy for invasive Gram-positive bacterial infections in children. *Pediatr Infect Dis J*. 2007;26(12):1128–1132.
26. Heger ML, Al-Sayyad B. Ceftaroline and daptomycin combination antibiotic therapy for a methicillin-resistant staphylococcus aureus liver abscess in a premature infant. *J Pediatr Pharmacol Ther*. 2022;27(8):754–759.
27. Kang JE, Byun J-H, Kim Y, Park SE. Successful treatment of vancomycin-resistant enterococcus bacteremia with a combination of daptomycin and tigecycline in an infant who underwent heart-lung transplantation. *Pediatric Infection Vaccine*. 2022;29(2):105–109.
28. Minotti C, Zuccon I, Priante E, et al. Daptomycin for treatment of *S. epidermidis* endocarditis in an extremely preterm neonate-outcome and perspectives. *Children (Basel)*. 2022;9(4):457.
29. Shigeta H, Tanaka K, Hoshina T, Kusuhara K. Successful daptomycin therapy for a premature neonate with left-sided infective endocarditis caused by Staphylococcus epidermidis. *Pediatr Neonatol*. 2021;62(4):456–457.
30. Chan JI, Noor A, Clauss C, et al. Methicillin-resistant Staphylococcus aureus endovascular infection in a neonate: prolonged, safe, and effective use of daptomycin and enoxaparin. *J Pediatr Pharmacol Ther*. 2020;25(1):68–74.
31. Sahin A, Dalgic N. Intravenous and intraventricular daptomycin plus intravenous linezolid treatment of an infant with vancomycin-resistant enterococci-induced ventriculoperitoneal shunt infection. *World Neurosurg*. 2019;124:328–330.
32. Sanchez J, Schneider A, Tretter JT, et al. Community-acquired MRSA pericarditis and mediastinitis in a previously healthy infant. *J Pediatr Intensive Care*. 2018;7(2):97–101.
33. Gawronski KM. Successful use of daptomycin in a preterm neonate with persistent methicillin-resistant Staphylococcus epidermidis bacteremia. *J Pediatr Pharmacol Ther*. 2015;20(1):61–65.
34. Tsironi EE, Zacharaki F, Grivea IN, et al. European ST80 community-associated methicillin-resistant Staphylococcus aureus orbital cellulitis in a neonate. *BMC Ophthalmol.* 2012;12:7.
35. Hussain A, Kairamkonda V, Jenkins DR. Successful treatment of meticillin-resistant Staphylococcus aureus bacteraemia in a neonate using daptomycin. *J Med Microbiol*. 2011;60(pt 3):381–383.
36. Porter KB, Lynch B, Mani CS. The use of daptomycin and linezolid to treat vancomycin-intermediate Staphylococcus haemolyticus infection in a premature infant. *J Pediatr Pharmacol Ther*. 2010;15(4):297–300.
37. Sarafidis K, Iosifidis E, Gikas E, et al. Daptomycin use in a neonate: serum level monitoring and outcome. *Am J Perinatol*. 2010;27(5):421–424.
38. Beneri CA, Nicolau DP, Seiden HS, Rubin LG. Successful treatment of a neonate with persistent vancomycin-resistant enterococcal bacteremia with a daptomycin-containing regimen. *Infect Drug Resist*. 2008;1:9–11.
39. Kinoshita T, Sahara S, Mihara Y, et al. A case of acute focal bacterial nephritis caused by methicillin-resistant Staphylococcus saprophyticus in a 13-year-old adolescent girl treated with daptomycin. *IDCases*. 2022;29:e01594.

40. Yozgat CY, Uzuner S, Ay Y, et al. Lifesaving treatment of aortic valve Staphylococcus aureus endocarditis: daptomycin and early surgical therapy. *J Pediatr Intensive Care*. 2021;10(4):298–302.
41. Hall AM, McTigue SM. Ceftaroline plus daptomycin for refractory methicillin-resistant Staphylococcus aureus bacteremia in a child. *J Pediatr Pharmacol Ther*. 2018;23(6):490–493.
42. Morris S, Gould K, Ferguson LP. The use of daptomycin to treat methicillin-resistant Staphylococcus epidermidis bacteremia in a critically ill child with renal failure. *J Pediatr Pharmacol Ther*. 2017;22(4):300–303.
43. Buyukcam A, Karadag Oncel E, Ozsurekci Y, et al. Vancomycin-resistant Enterococcus bacteremia in a child with acute myeloid leukemia: successful treatment with daptomycin. *Arch Argent Pediatr*. 2016;114(6): e432–e435.
44. Prabhudesai S, Kanjani A, Nambi PS, et al. Successful use of high-dose daptomycin in a child with Staphylococcus aureus endocarditis. *Pediatr Infect Dis J*. 2016;35(5):517–518.
45. Billups KL, Stultz JS. Successful daptomycin use in a pediatric patient with acute, bilateral osteomyelitis caused by methicillin-resistant Staphylococcus aureus. *J Pediatr Pharmacol Ther*. 2015;20(5):397–402.
46. Jalal Z CF, Roubertie F, Iriart X, Thambo J. Pediatric case of MRSA right-sided infective endocarditis with septic pulmonary embolism successfully treated by daptomycin in combination with gentamicin and rifampin. *J Pediatr Infect Dis*. 2013;8(3):139–142.
47. Mutschler M, Trojan S, Defosse JM, et al. Severe sepsis caused by a linezolid-resistant Enterococcus faecium in a 10-year-old girl after multiple trauma. *Int J Infect Dis*. 2013;17(6):e466–467.
48. Erturan G, Holme H, Smith R, et al. Successful use of daptomycin in Panton-Valentine leucocidin positive Staphylococcus aureus paediatric osteomyelitis. *Int J Surg Case Rep*. 2012;3(7):238–241.
49. Fossati M, Cappelli B, Biral E, et al. Fatal vancomycin- and linezolid-resistant Enterococcus faecium sepsis in a child undergoing allogeneic haematopoietic stem cell transplantation for beta-thalassaemia major. *J Med Microbiol*. 2010;59(pt 7):839–842. doi:10.1099/jmm.0.018598-0
50. Jaspan HB, Brothers AW, Campbell AJ, et al. Multidrug-resistant Enterococcus faecium meningitis in a toddler: characterization of the organism and successful treatment with intraventricular daptomycin and intravenous tigecycline. *Pediatr Infect Dis J*. 2010;29(4):379–381.
51. Jacobson LM, Milstone AM, Zenilman J, et al. Daptomycin therapy failure in an adolescent with methicillin-resistant Staphylococcus aureus bacteremia. *Pediatr Infect Dis J*. 2009;28(5):445–447.
52. Akins RL, Haase MR, Levy EN. Pharmacokinetics of daptomycin in a critically ill adolescent with vancomycin-resistant enterococcal endocarditis. *Pharmacotherapy*. 2006;26(5):694–698.
53. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother*. 2004;48(1):63–68.
54. Wei XC, Zhao MF, Li X, Xiao X. Pharmacokinetic/pharmacodynamic analysis of daptomycin against Staphylococcus aureus and Enterococcus faecium in pediatric patients by Monte Carlo Simulation. *J Clin Pharmacol*. 2020;60(6):768–774.
55. Werner G, Neumann B, Weber RE, et al. Thirty years of VRE in Germany – "expect the unexpected": The view from the National Reference Centre for Staphylococci and Enterococci. *Drug Resist Updat*. 2020;53:100732.
56. Bradley JS, Benziger D, Bokesch P, Jacobs R. Single-dose pharmacokinetics of daptomycin in pediatric patients 3-24 months of age. *Pediatr Infect Dis J*. 2014;33(9):936–9.