Evolving Epidemiology and Treatment of Invasive *Staphylococcus aureus* Infections in Children

Sheldon L. Kaplan, MD

Texas Children's Hospital®

BCM
Baylor College of Medicine

Pediatrics

Disclosures

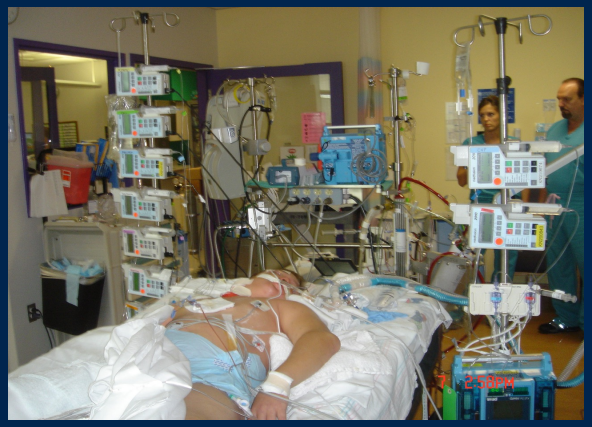
- Pfizer-Grant for Investigator initiated multicenter pediatric surveillance study of invasive pneumococcal infections.
- Pfizer-Contract for CAP study

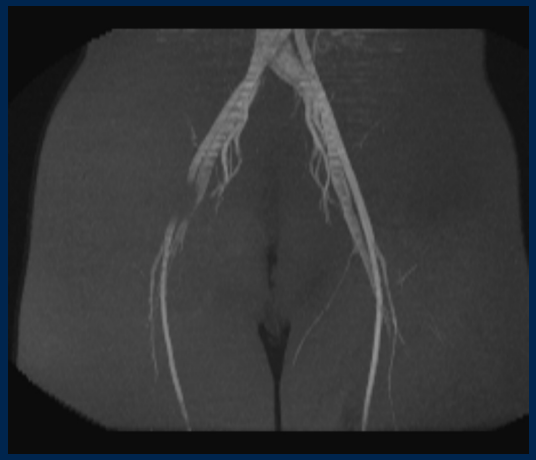
Goals

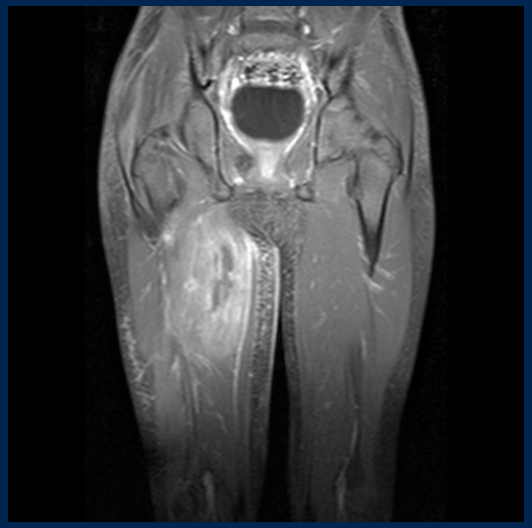
- Discuss current epidemiology of invasive *S. aureus* infections in children and the susceptibilities of isolates for the commonly used antibiotics.
- Discuss current antibiotics and routes of administration recommended for treating *S. aureus* infections in children and what agents maybe available in the future.

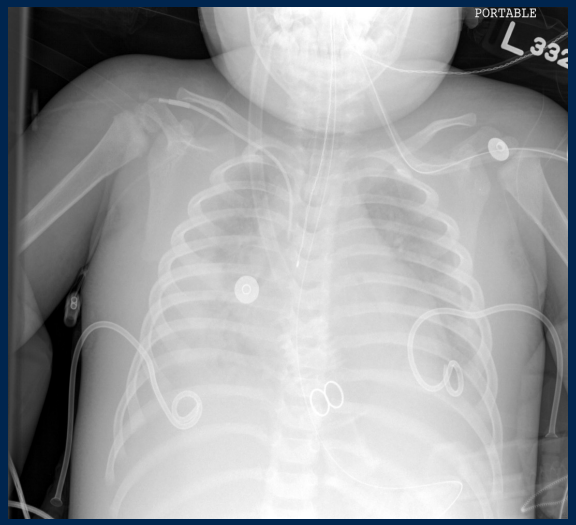
Invasive *S. aureus* Infections

- Osteomyelitis-multiple sites and DVT
- Pyomyositis/myositis
- Bacteremia/septic shock
- Purpura fulminans
- Pneumonia/empyema
- Necrotizing pneumonia
- Necrotizing fasciitis
- Epidural abscess
- Orbital Cellulitis/Abscess
- Deep Abscesses



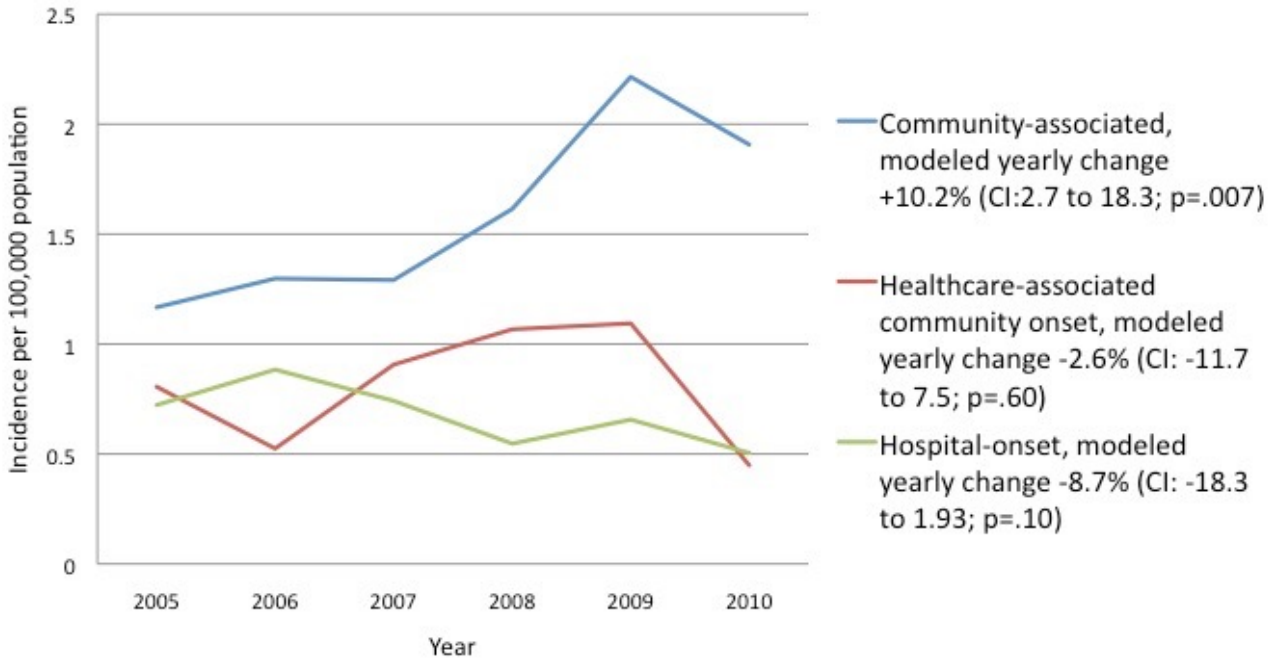






Invasive methicillin-resistant *Staphylococcus aureus* infections among children, 2005-2010

Figure . Incidence of invasive MRSA infections among children (≥90 days of age),* by epidemiological classification, Active Bacterial Core Surveillance, 2005-2010



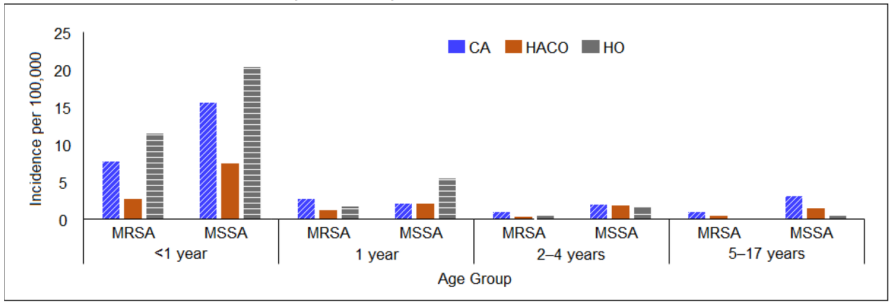
*Incidence rates of late-onset invasive MRSA infections among infants < 90 days of age were examined separately.

Iwamoto et al. *Pediatrics* 2013;132:e817-824

Emerging Infections Program
Healthcare-Associated Infections Community Interface Report
Invasive *Staphylococcus aureus*, 2020

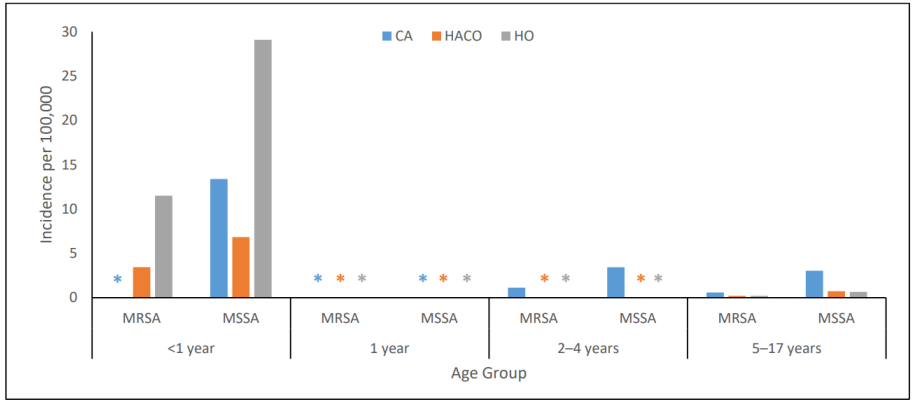
HAIC / EIP Network Report: Invasive *Staphylococcus aureus*, 2016

Incidence[a] of Invasive *Staphylococcus aureus*[b], by Epidemiologic Class, Age Group, and Methicillin-Resistance Status, Children, 2016



a Incidence (no. per 100,000 population per year) calculated using 2016 U.S. Census Data
b MSSA case counts multiplied by 1.2 for one site

Incidence[a,b] of Invasive *Staphylococcus aureus*, by Epidemiologic Class, Pediatric Age Groups, and Methicillin-Resistance Status, 2020



* Case count < 5

https://www.cdc.gov/hai/eip/pdf/2016-MRSA-Report-508.pdf
https://www.cdc.gov/hai/eip/pdf/2020-MRSA-Report-508.pdf

Texas Children's Hospital
BCM Baylor College of Medicine

Analysis of Invasive Community-Acquired Methicillin-Susceptible *Staphylococcus aureus* Infections During a Period of Declining Community Acquired Methicillin-Resistant *Staphylococcus aureus* Infections at a Large Children's Hospital

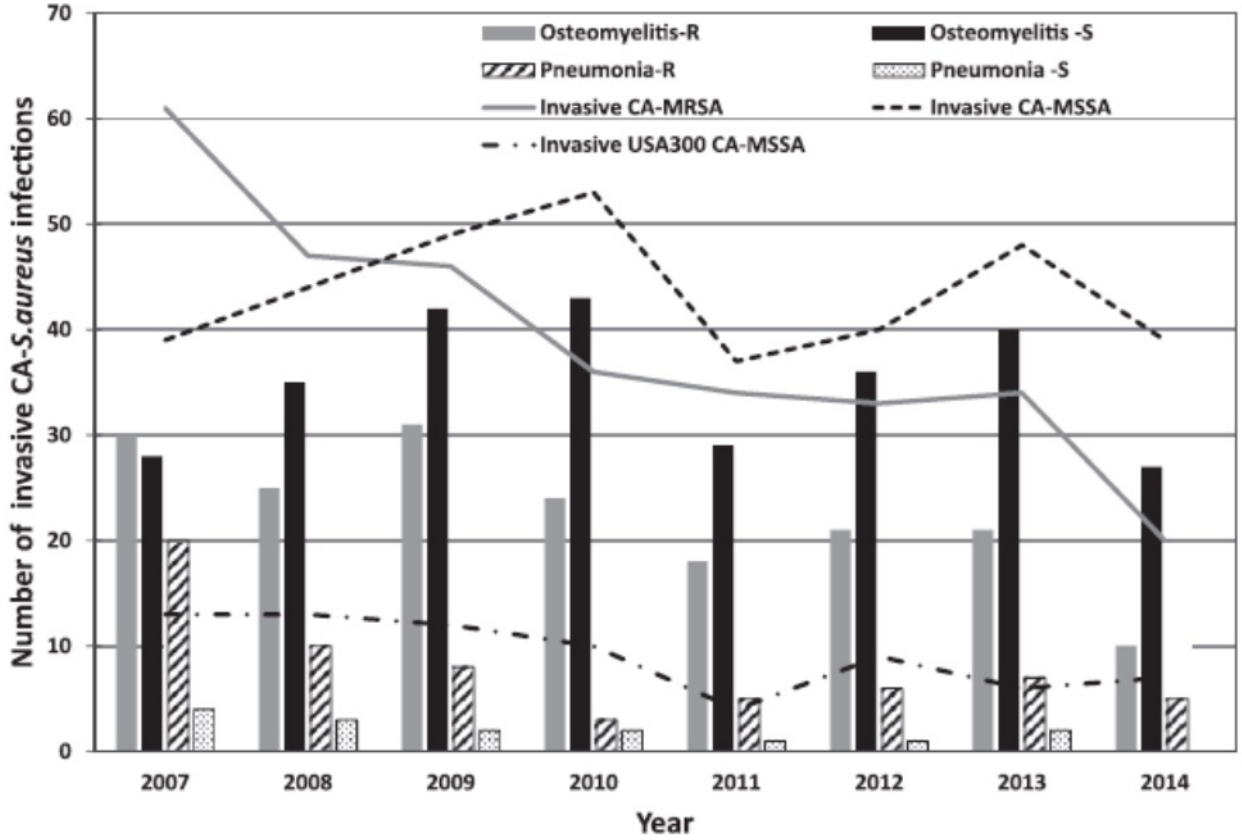
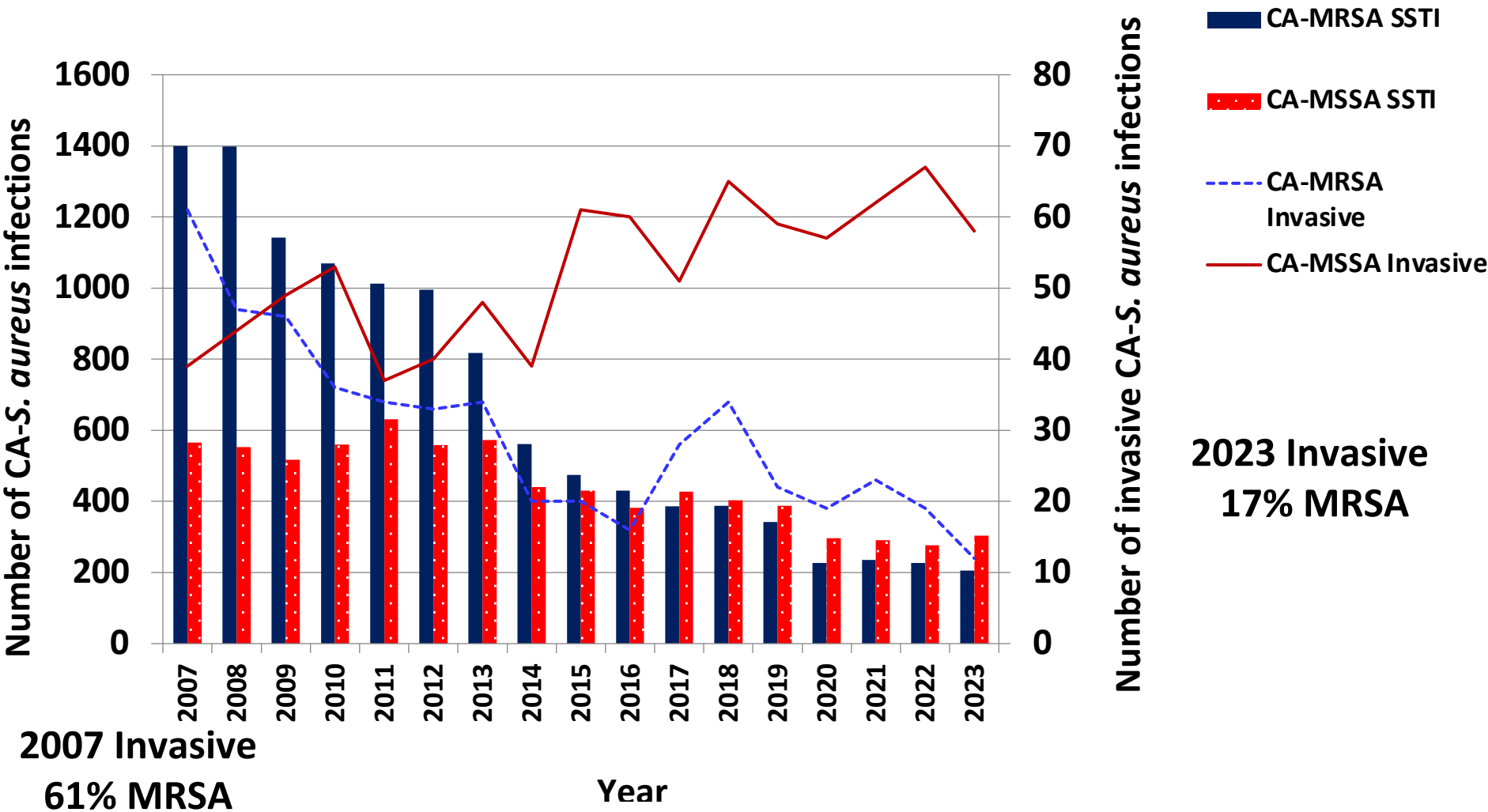


FIGURE 2. Decreasing MRSA as a cause of invasive *S. aureus* infections at Texas Children's Hospital, 2007–2014. χ^2 for trend: decline of invasive CA-MRSA/annual hospital admissions: $P < 0.0001$. χ^2 for trend decline of invasive USA300 CA-MSSA/annual hospital admissions, $P < 0.03$; decline of invasive USA300 among invasive CA-MSSA, $P = 0.008$.

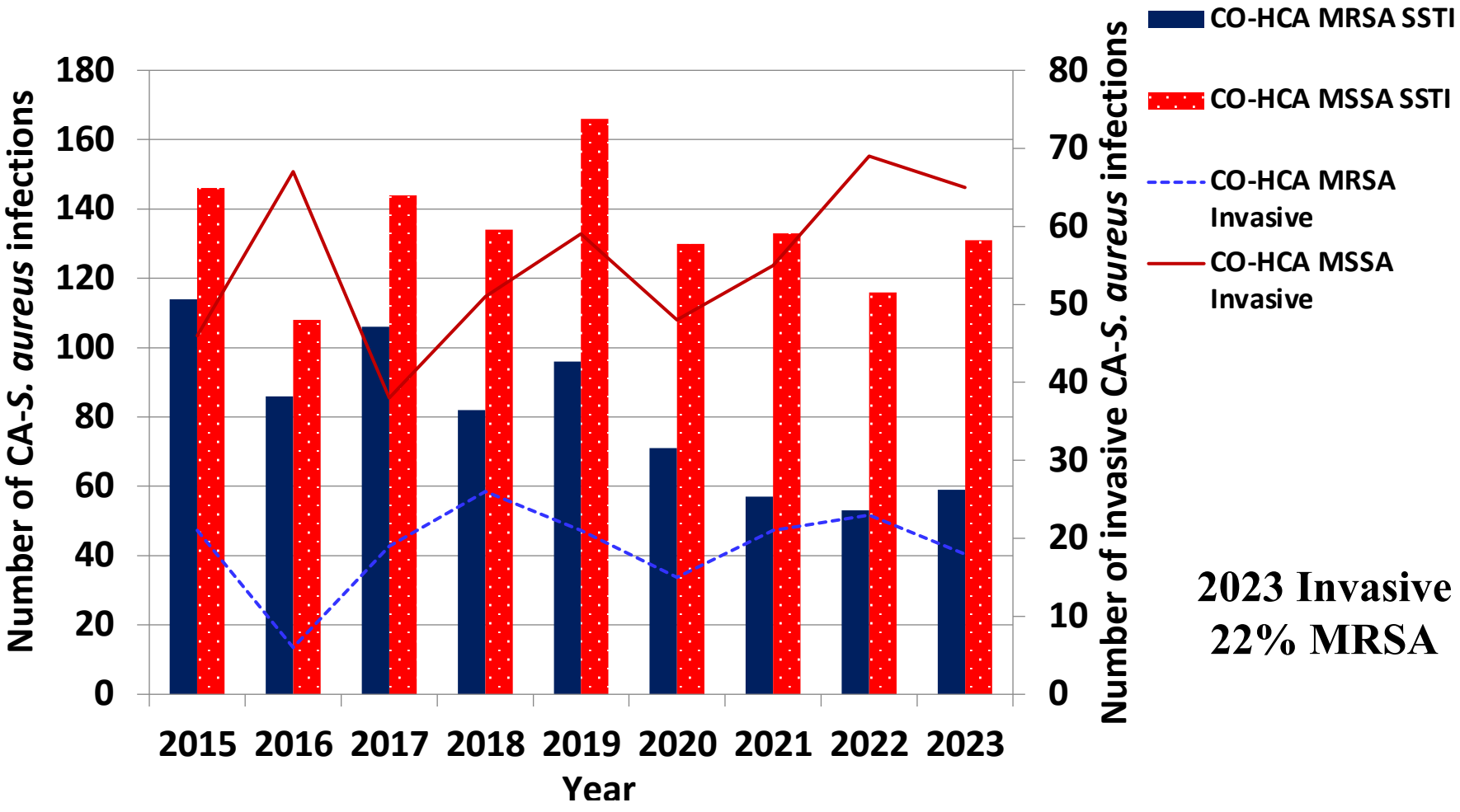
Hulten et al. *Pediatr Infect Dis J* 2018;37:235-241

Community-Associated *Staphylococcus aureus* Infections-Texas Children's Hospital



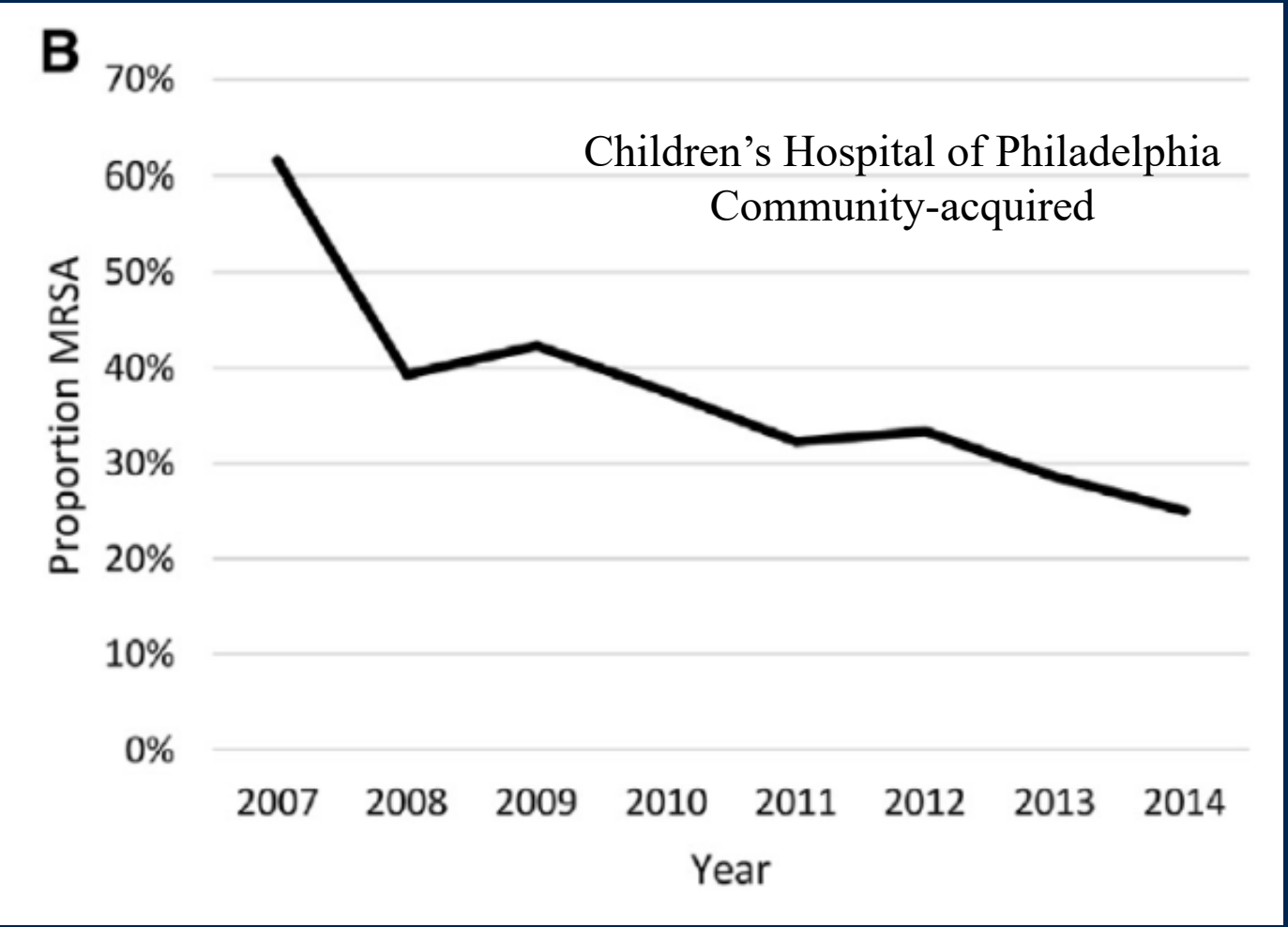
Courtesy Kristina G. Hulten, PhD

Community-Onset Healthcare Associated *Staphylococcus aureus* Infections-TCH



Courtesy Kristina G. Hulten, PhD

Risk Factors for Complications in Children with *Staphylococcus aureus* Bacteremia



Hamdy et al. *J Pediatr* 2019;208:214-220

Trends in pediatric community-onset *Staphylococcus aureus* antibiotic susceptibilities over a five-year period in a multihospital health system

Community-onset Invasive and SSTI

Baltimore

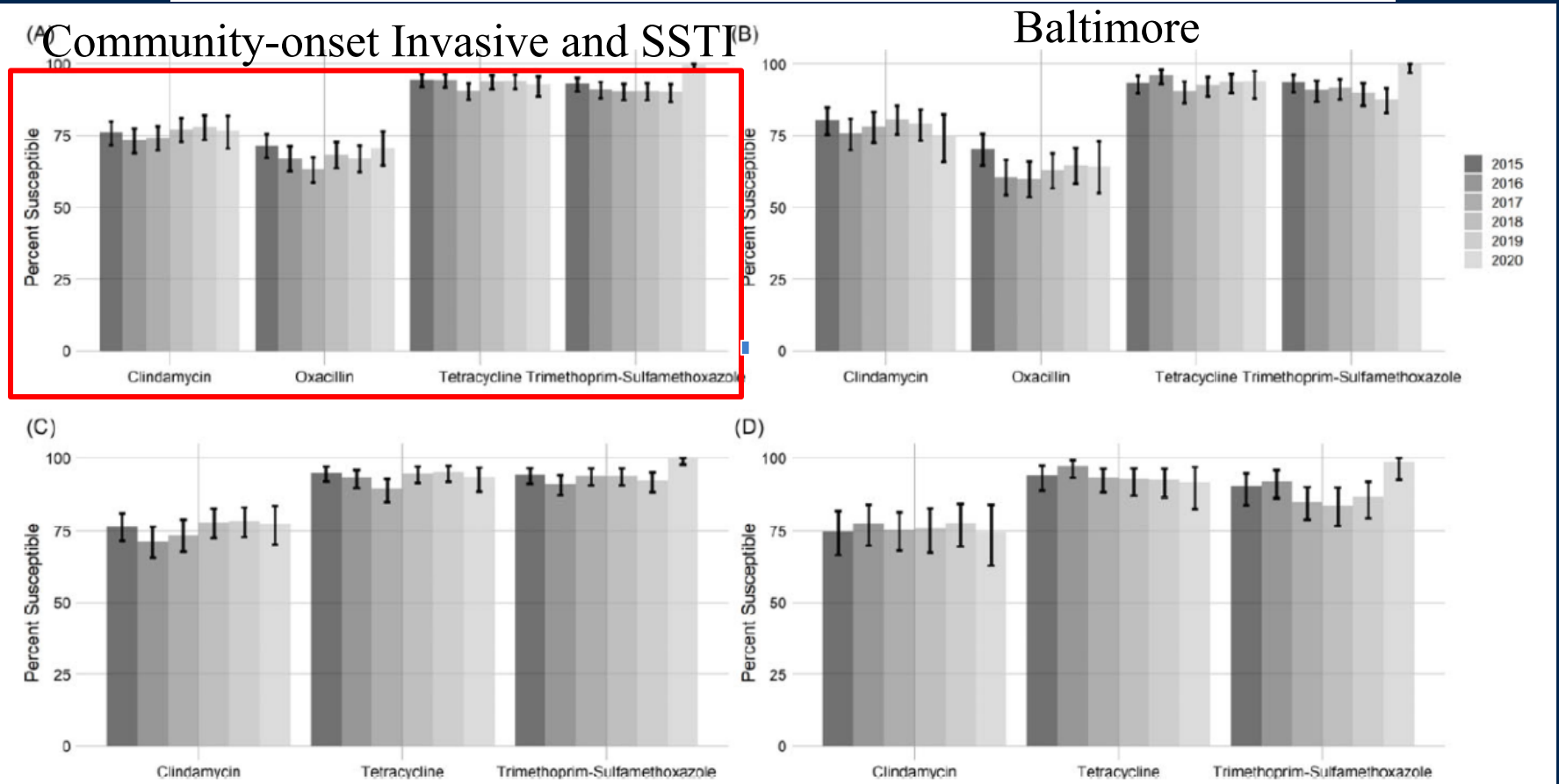
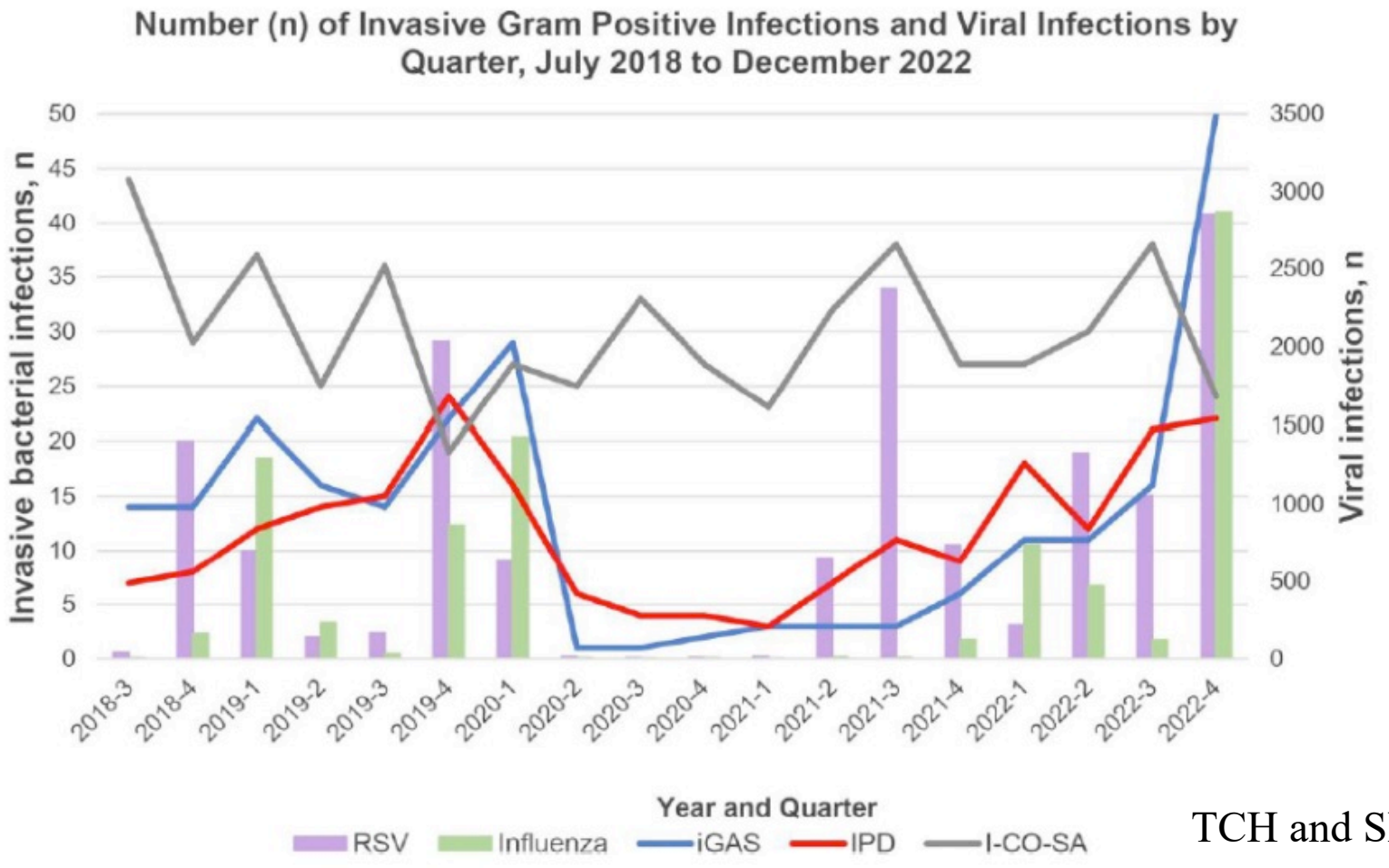


Fig. 1. Percentage with antibiotic susceptibility with 95% confidence intervals during the study period in (A) community-onset *S. aureus* cultures; (B) community-onset, out-patient-managed *S. aureus* cultures, (C) community-onset MSSA cultures; and (D) community-onset MRSA cultures.

Overall 84% of Invasive Infections were MSSA

Prochaska et al. *Antimicrobial Stewardship & Healthcare Epidemiology* 2023;3:e12,1-4

Invasive Community-Onset Gram-Positive Infections From July 2018 Through December 2022 at 2 Children's Hospitals



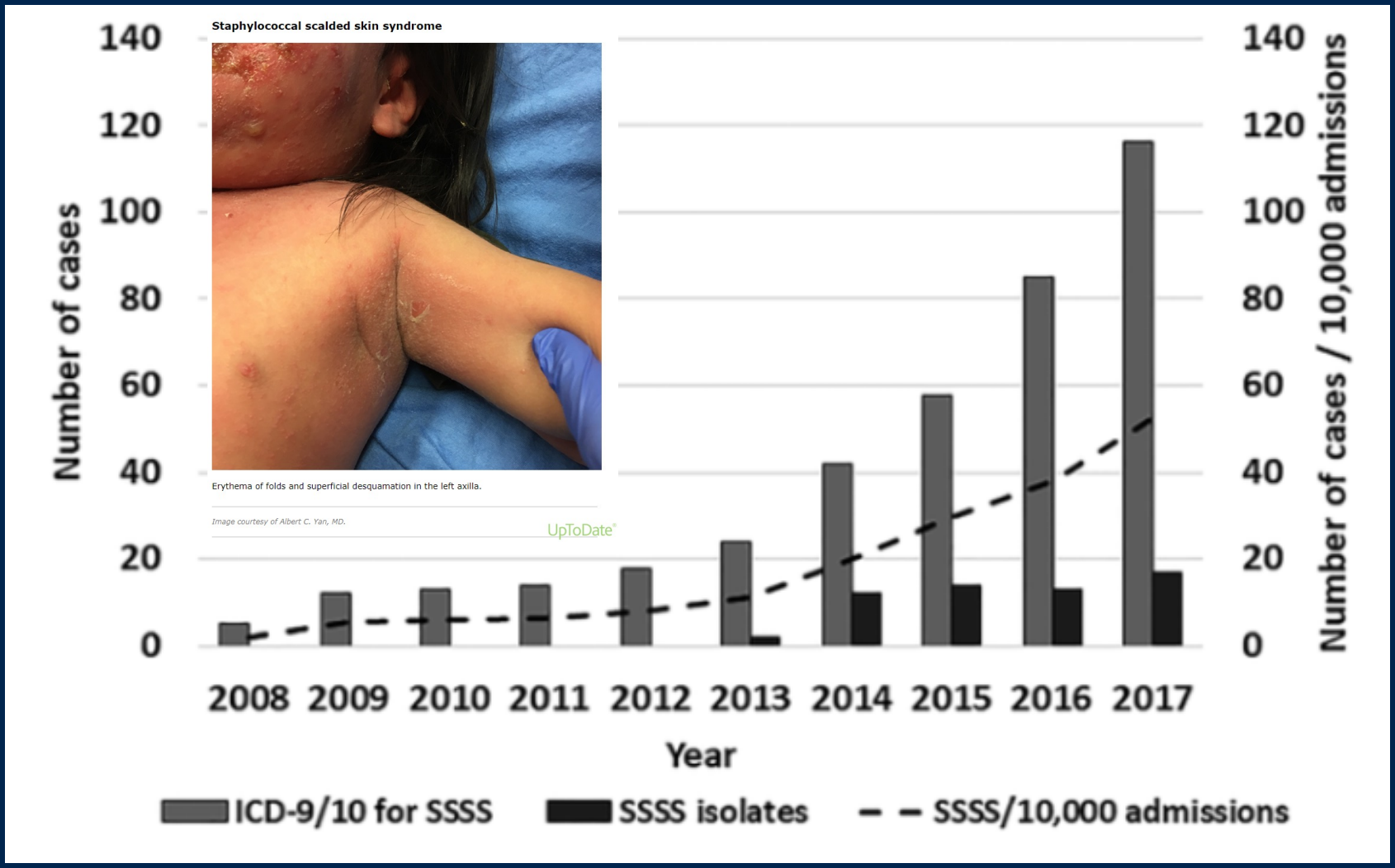
TCH and SLCH

Engstrom et al. *Open Forum Infect Dis* 2023;10:ofad563

Texas Children's Hospital

BCM Baylor College of Medicine

Increasing Numbers of Staphylococcal Scalded Skin Syndrome Cases Caused by ST121 in Houston, Texas



Hulten et al. *Pediatr Infect Dis J* 2020;39:30-34

Texas Children's Hospital®

BCM Baylor College of Medicine

Clinical Characteristics and Outcomes of *Staphylococcus aureus* Implant-associated Infections in Children

TABLE 1. Clinical Characteristics of Patients With *Staphylococcus aureus* IAIs at TCH, January 2008–June 2016

Demographic or Characteristic	All IAIs*, n = 47 (%)	MSSA IAIs, n = 34 (%)	MRSA IAIs, n = 13 (%)	*P*
Sex, n (%)				
Male	25 (53)	19 (55.9)	6 (46.2)	0.75
Age (years), median (range)	12.1 (1–20.2)	12.3 (1.3–20.2)	10.3 (1–18.6)	0.92
Ethnicity†				0.53
Asian	1 (2.2)	0	1 (7.7)	
Black	4 (8.7)	3 (9)	1 (7.7)	
Caucasian	23 (50)	17 (51.5)	6 (46.2)	
Hispanic	18 (39.1)	13 (39.4)	5 (38.5)	
Time to infection, n (%)				0.38
0–30 days	12 (25.5)	8 (23.5)	4 (30.8)	
31–90 days	18 (38.3)	14 (41.2)	4 (30.8)	
91–365 days	14 (29.8)	11 (32.4)	3 (23.1)	
>365 days	3 (6.4)	1 (2.9)	2 (15.4)	
Type of implant, n (%)				0.7
Orthopedic spinal rod	22 (46.8)	16 (47.1)	6 (46.2)	
Other orthopedic hardware‡	19 (40.4)	12 (35.3)	7 (53.9)	
VNS	3 (6.4)	3 (8.8)	0	
Baclofen pump	2 (4.3)	2 (5.9)	0	
Cochlear implant	1 (2.1)	1 (2.9)	0	

Mandibular distractor

Osia bone conduction hearing device

Foster et al. *Pediatr Infect Dis J* 2019;38:808-811

Staphylococcus aureus Diagnosis Present

- Cultures
- Rapid identification of *S. aureus*, MSSA vs MRSA in blood cultures positive for Gram positive cocci in clusters
- Molecular tests-body fluid PCR to detect *S. aureus* (MSSA vs MRSA) in normally sterile fluids such as pleural fluid, synovial fluid.

Staphylococcus aureus Treatment Present

Methicillin-susceptible	Methicillin-resistant
-Nafcillin/oxacillin	-Vancomycin
-Cefazolin	-Clindamycin
-Cephalexin	-TMP-SMX
-Clindamycin*	-Linezolid
-Trimethoprim-sulfamethoxazole*	-Daptomycin
*penicillin allergic	-Ceftaroline

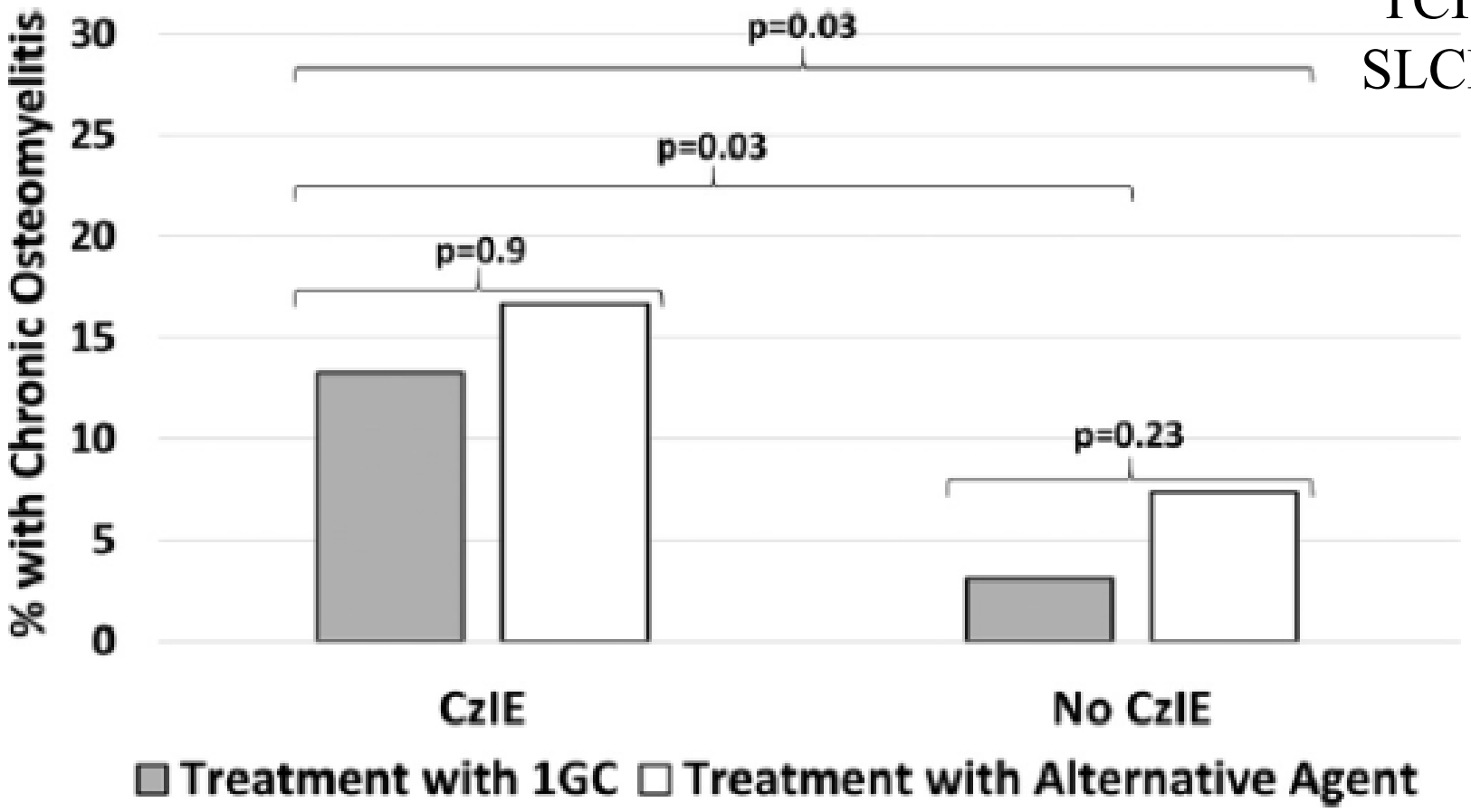
Table 3.54 Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections

II. Methicillin-susceptible, penicillin-resistant *S aureus* (MSSA)

Drugs of choice:	Nafcillin or oxacillin[a] Cefazolin	← Leukopenia Infusion pain
	Clindamycin	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
Alternatives:	Vancomycin	Only for patients with a serious penicillin and cephalosporin allergy
	Ampicillin + sulbactam	For patients with polymicrobial infections caused by susceptible isolates.

2021-2024 Red Book

Cefazolin Inoculum Effect and Methicillin-Susceptible *Staphylococcus aureus* Osteoarticular Infections in Children



McNeil et al. *Antimicrob Agents Chemother* 2020;64:e0073-20

Texas Children's Hospital

BCM Baylor College of Medicine

Cefazolin Inoculum Effect and Methicillin-Susceptible *Staphylococcus aureus* Osteoarticular Infections in Children

TABLE 5 Multivariable analyses of risk factors for MSSA chronic osteomyelitis[a]

Factor	Multivariable *P* value	Adjusted OR	95% CI
Bone abscess	0.54	1.58	0.37–6.7
Positive blood culture	0.09	4.1	0.8–20.26
≥2 surgical procedures	0.01	6.99	1.58–31.1
Delayed first source control	0.03	2.59	1.16–11.11
*agr*III	0.04	1.71	1.03–7.81
CzIE	0.03	13.4	1.1–18.21

McNeil et al. *Antimicrob Agents Chemother* 2020;64:e0073-20

III. Methicillin-resistant *S aureus* (MRSA; oxacillin MIC, 4 µg/mL or greater)

B. Community-associated (not multidrug resistant)

	Vancomycin ± gentamicin[a]	For life-threatening infections or endovascular infections including those complicated by venous thrombosis.
Drugs of choice:	Clindamycin (if strain susceptible)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole Doxycycline (susceptible)	For skin or soft tissue infections
	Vancomycin	For serious infections
Alternative:	Linezolid	For serious infections caused by clindamycin resistant isolates in patients with renal dysfunction or those intolerant of vancomycin.

[a]Prosthetic valve endocarditis

2021-2024 Red Book

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Pediatrics

67. Data are limited to guide vancomycin dosing in children. IV vancomycin 15 mg/kg/dose every 6 h is recommended in children with serious or invasive disease **(B-III).**

68. The efficacy and safety of targeting trough concentrations of 15–20 μg/mL in children requires additional study but should be considered in those with serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (ie, necrotizing fasciitis) **(B-III).**

Liu et al. *Clin Infect Dis* 2011;52:285-292

Healthcare-associated *Staphylococcus aureus* Bacteremia in Children

Evidence for Reverse Vancomycin Creep and Impact of Vancomycin Trough Values on Outcome

McNeil et al. *Pediatr Infect Dis J* 2016;35:263-268

The Influence of the Route of Antibiotic Administration, Methicillin Susceptibility, Vancomycin Duration and Serum Trough Concentration on Outcomes of Pediatric *Staphylococcus aureus* Bacteremic Osteoarticular Infection

McNeil et al. *Pediatr Infect Dis J* 2017;36:572-577

Evaluation of Target Attainment of Vancomycin Area Under the Curve in Children With Methicillin-Resistant *Staphylococcus Aureus* Bacteremia

Hahn et al. *Ther Drug Monit* 2015;37:619-625.

Vancomycin Treatment Failure in Children With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Regen et al. *J Pediatr Pharmacol Ther* 2019;24:312-319

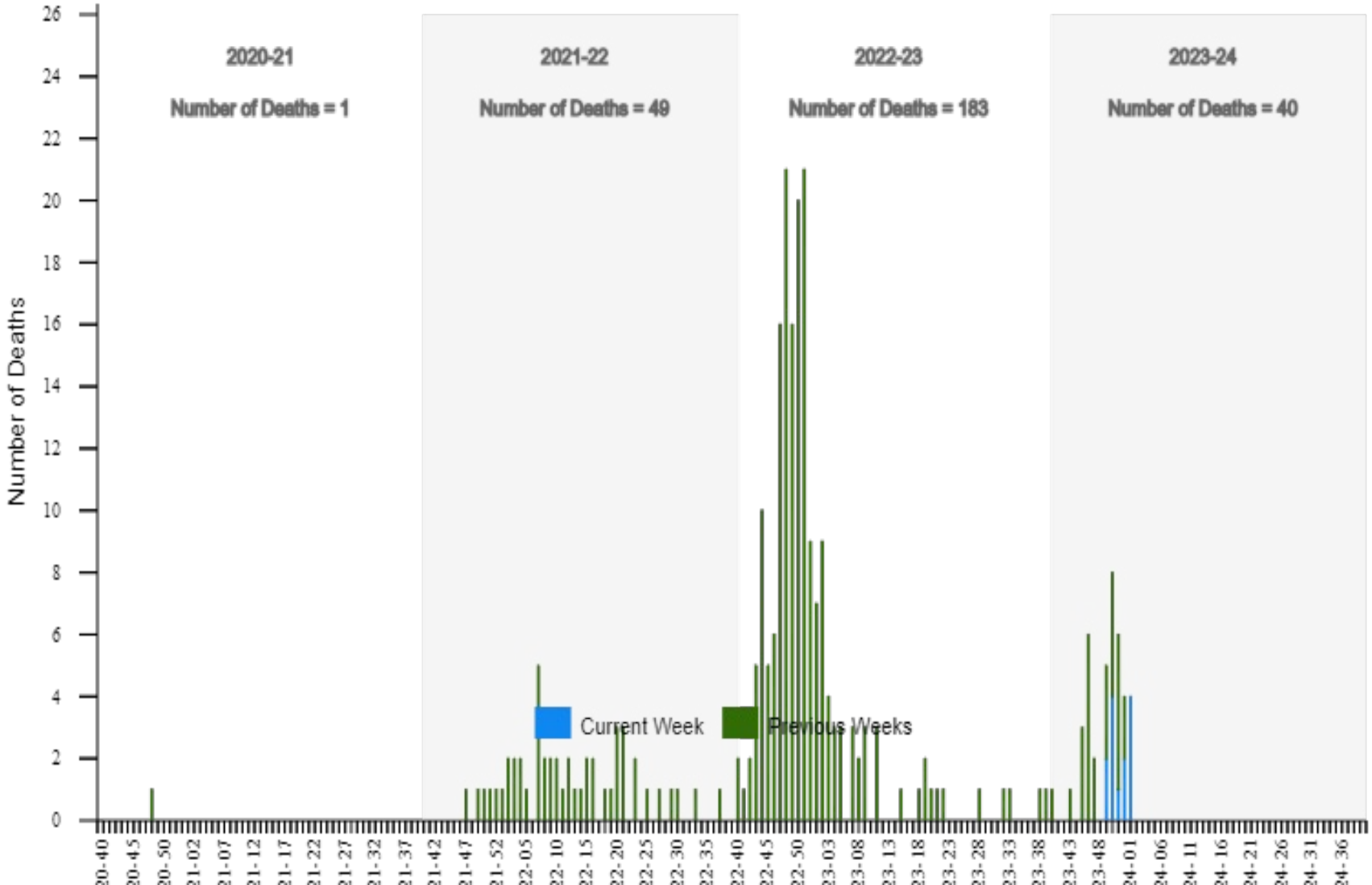
Vancomycin Monitoring

vancomycin exposure. The area-under-the-curve to minimum inhibitory concentration (AUC/MIC) has been identified as the most appropriate pharmacokinetic/pharmacodynamic (PK/PD) target for vancomycin in adult patients with MRSA. Although there are limitations in prospective outcomes data in pediatric patients with serious MRSA infections, the most recent consensus guideline from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists recommend AUC guided therapeutic monitoring, preferably with Bayesian estimation, for all pediatric age groups receiving vancomycin.[1,2,3] This estimation accounts for developmental changes of vancomycin clearance from newborn to adolescent. Dosing in children should be designed to achieve an AUC of 400 to 600 μg-hour/L (assuming MIC of 1) and/or trough levels <15 μg/mL to minimize AKI risks. Bayesian estimation can be completed with 2 levels, with one level being recommended 1 to 2 hours after end of vancomycin infusion and the second level being drawn 4 to 6 hours after end of infusion. Levels can be obtained as early as after the second dose. Software to assist with these calculations is available online and for purchase. It is recommended to avoid AUC >800 and troughs >15. Most children younger than 12 years will require higher doses to achieve optimal AUC/MIC compared with older children.

FLUVIEW interactive

CDC

Influenza-Associated Pediatric Deaths
by Week of Death, 2020-21 season to 2023-24 season



Vancomycin Monotherapy May Be Insufficient to Treat Methicillin-resistant *Staphylococcus aureus* Coinfection in Children With Influenza-related Critical Illness

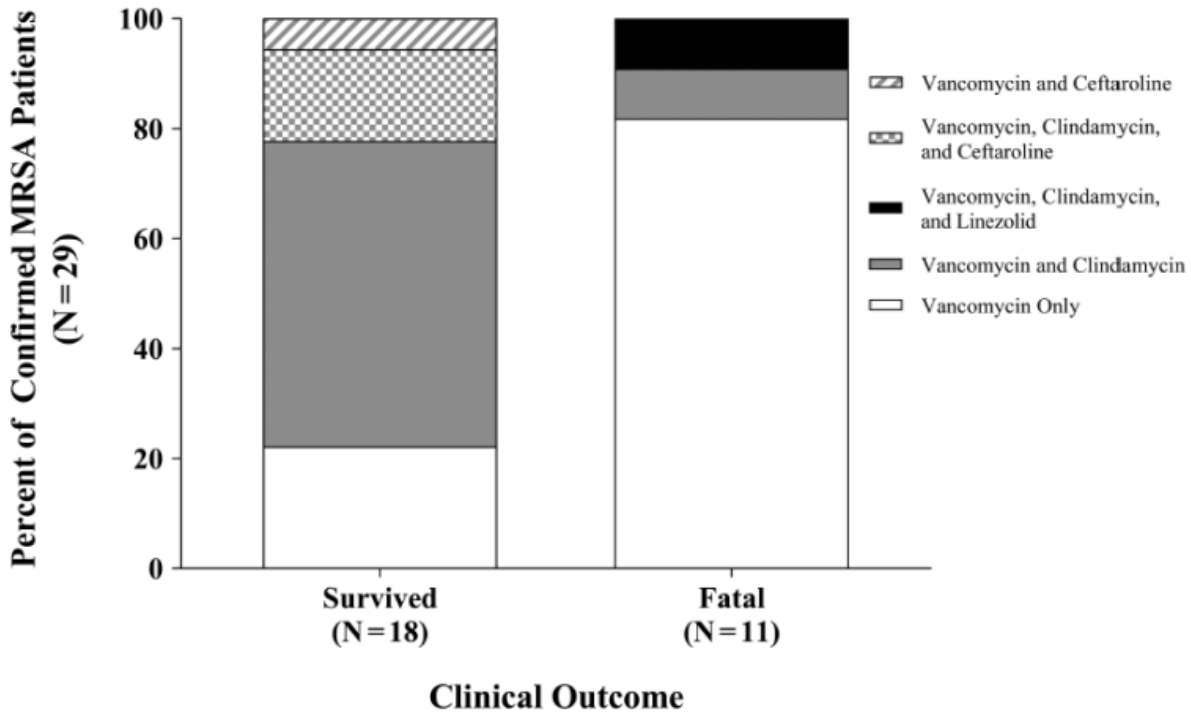


Figure 3. Comparison of vancomycin only to vancomycin with additional anti-methicillin-resistant *Staphylococcus aureus* agent(s) within the first 24 hours of pediatric intensive care unit admission stratified by survival The relative risk (RR) of mortality in the vancomycin only group was 5.54 (95% confidence interval, 1.4–21.3). Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Randolph et al. *Clin Infect Dis* 2019;68:365-372

III. Methicillin-resistant *S aureus* (MRSA; oxacillin MIC, 4 µg/mL or greater)

B. Community-associated (not multidrug resistant)

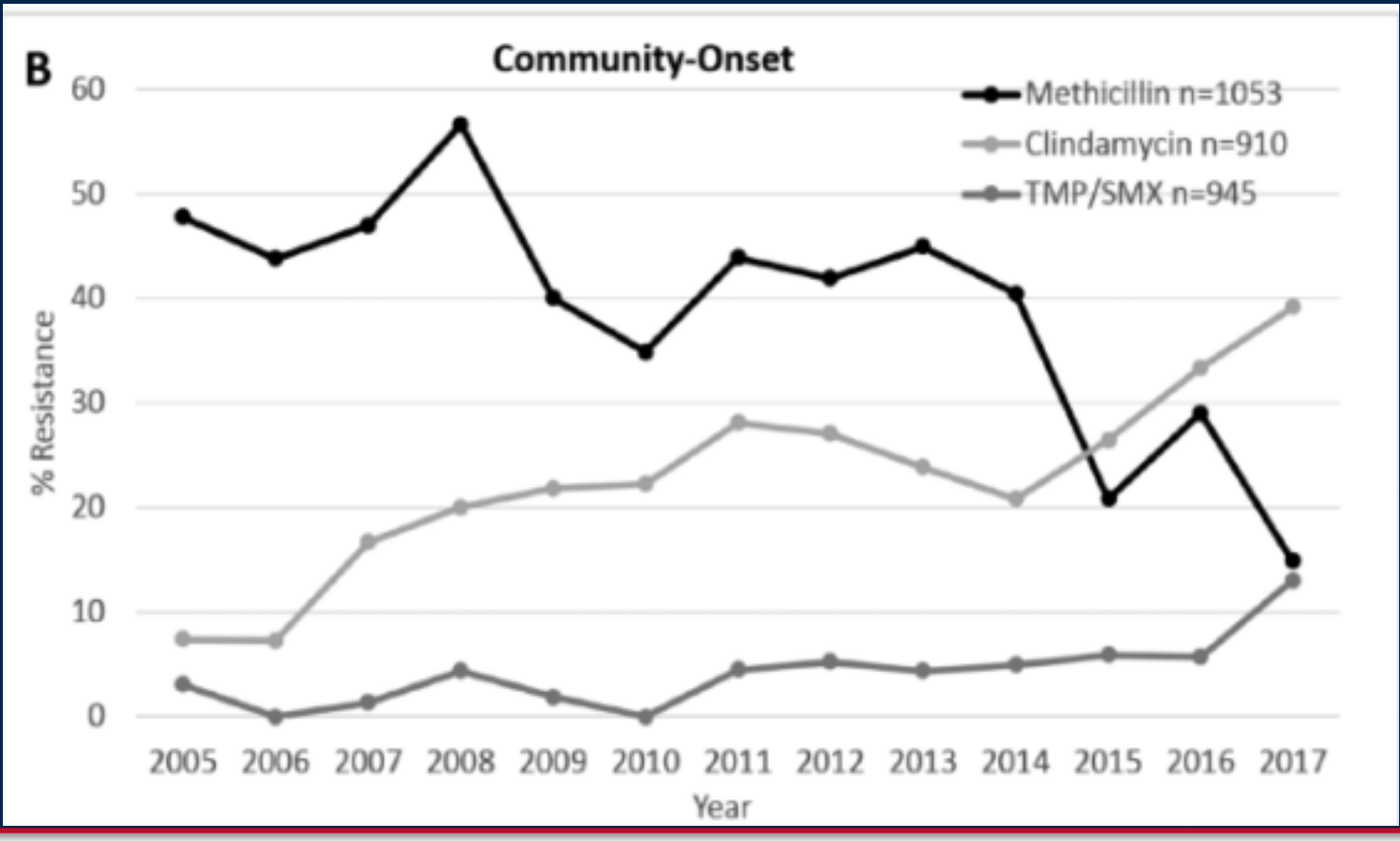
	Vancomycin ± gentamicin[a]	For life-threatening infections or endovascular infections including those complicated by venous thrombosis.
Drugs of choice:	Clindamycin (if strain susceptible)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole Doxycycline (susceptible)	For skin or soft tissue infections
	Vancomycin	For serious infections
Alternative:	Linezolid	For serious infections caused by clindamycin resistant isolates in patients with renal dysfunction or those intolerant of vancomycin.

[a]Prosthetic valve endocarditis

2021-2024 Red Book

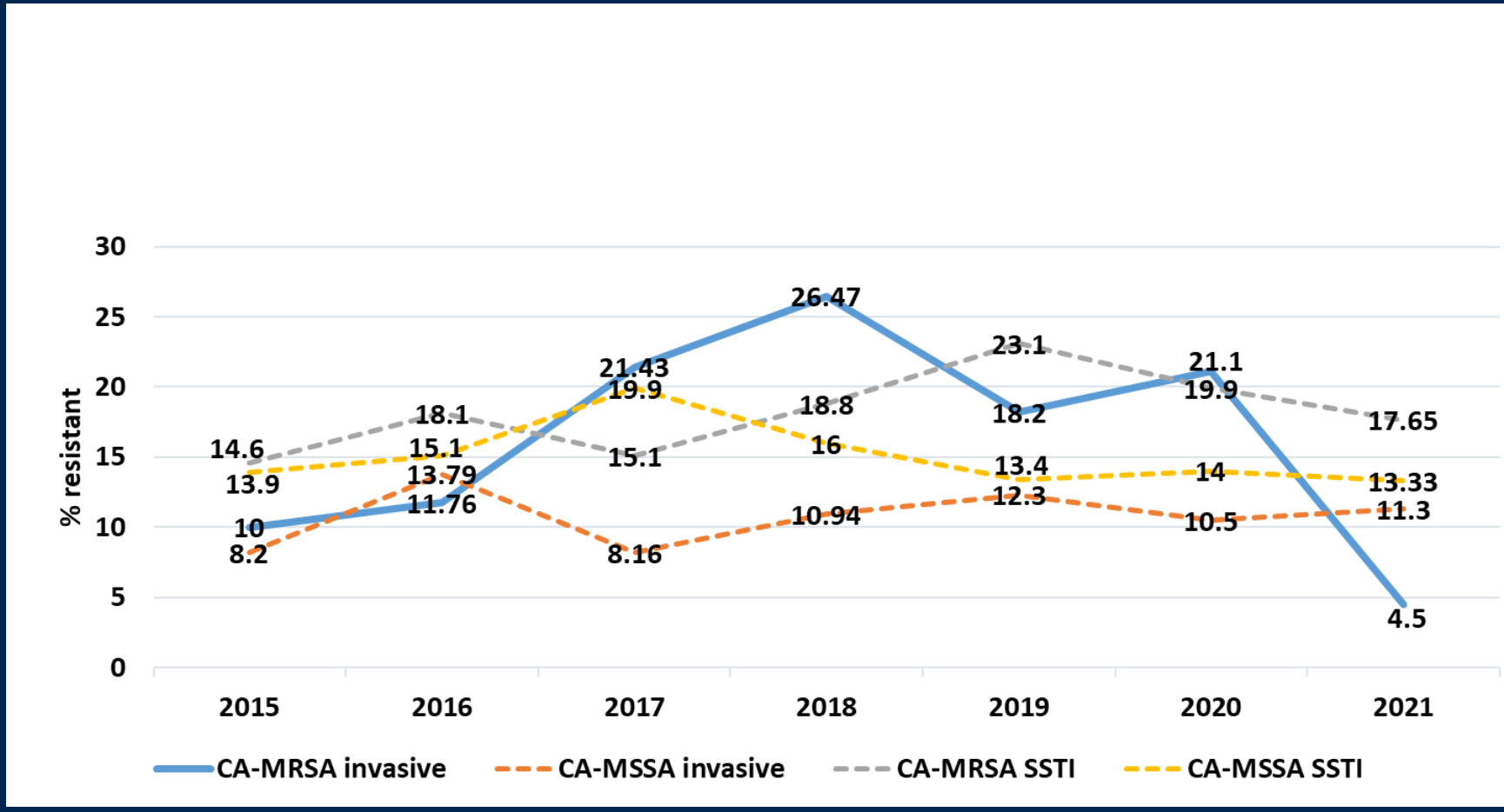
Increasing Clindamycin and Trimethoprim-Sulfamethoxazole Resistance in Pediatric *Staphylococcus aureus* Infections

Baltimore



Khamash et al. *J Pediatr Infect Dis Soc* 2019;8:351-353

Clindamycin Resistant *Staphylococcus aureus* TCH



Pediatrics

Macias et al. Submitted

Texas Children's Hospital

BCM Baylor College of Medicine

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

Table 4. Antibiotic Choice and Duration of Therapy for *Uncomplicated* Pediatric Acute Hematogenous Osteomyelitis (AHO) Caused by *Staphylococcus aureus*[a,b]

Pathogen	Parenteral Therapy	Oral Convalescent Therapy	Duration[c]
Staphylococcus aureus, methicillin susceptible	Preferred[d]: Cefazolin; Semi-synthetic penicillin[e], eg, oxacillin and nafcillin	Preferred: Cephalexin	3 to 4 weeks if uncomplicated
	Alternatives[d]: Clindamycin; Vancomycin; Ceftaroline	Alternative: Clindamycin	3 to 4 weeks if uncomplicated
S. aureus, methicillin-resistant, susceptible to clindamycin	Preferred: Clindamycin	Preferred: Clindamycin	3 to 4 weeks if uncomplicated
	Alternatives: Vancomycin; Daptomycin; Ceftaroline; Linezolid	Alternatives[f]: Linezolid	No data
S. aureus, methicillin-resistant, resistant to clindamycin	Preferred: Vancomycin	Preferred: Linezolid	No data
	Alternatives: Daptomycin; Ceftaroline; Linezolid	Alternatives: Insufficient clinical data for the treatment of AHO to recommend other oral antibiotics with in vitro activity against *S. aureus*	No data

J Pediatr Infect Dis Soc 2021;10:801-844

Experience With Linezolid Therapy in Children With Osteoarticular Infections

- Chang Gung Children's Hospital in Taoyuan, Taiwan
- 13 children (3 months to 14 years old) received linezolid for osteoarticular infections
- MRSA in 11
- Step down therapy-11; IV followed by oral in 3 others
- Median duration: 20 days (range 9-36 days)
- 11 cured
- 2 developed anemia

Chen et al. *Pediatr Infect Dis J* 2007;26:985-988.

A Multicenter, Randomized, Observer-blinded, Active-controlled Study Evaluating the Safety and Effectiveness of Ceftaroline Compared With Ceftriaxone Plus Vancomycin in Pediatric Patients With Complicated Community-acquired Bacterial Pneumonia

TABLE 3. Clinical Outcome and Clinical Response in the MITT Population

	Ceftaroline Fosamil (N = 29), n (%)	Comparator (N = 9), n (%)
Clinical outcome EOT		
Clinical cure	24 (82.8)	7 (77.8)
Difference, % (95% CI)	5.0 (−19.9, 40.3)	
Clinical failure	3 (10.3)	0
Indeterminate	2 (6.9)	2 (22.2)
Clinical outcome TOC		
Clinical cure	26 (89.7)	9 (100)
Difference, % (95% CI)	−10.3 (−26.7, 21.0)	
Clinical failure	3 (10.3)	0
Indeterminate	0	0
Clinical response at study day 4		
Responder	15 (51.7)	6 (66.7)
Difference, % (95%, CI)	−14.9 (−44.6, 22.0)	
Nonresponder	11 (37.9)	3 (33.3)
Incomplete data	3 (10.3)	0
Clinical stability at study day 4		
Stability	6 (20.7)	2 (22.2)
Difference, % (95% CI)	−1.5 (−37.2, 23.8)	
No stability	22 (75.9)	7 (77.8)
Incomplete data	1 (3.4)	0

Blumer et al. *Pediatr Infect Dis J* 2016;35:760-766

CASE REPORT

Ceftaroline Fosamil Use in 2 Pediatric Patients With Invasive Methicillin-Resistant *Staphylococcus aureus* Infections

Amanda W. Williams, PharmD,[1] Patrick M. Newman, PharmD,[1] Sara Ocheltree, MD,[2] Rachel Beaty, PharmD,[1,3] and Ali Hassoun, MD[2]

[1]Department of Pharmacy, Huntsville Hospital for Women and Children, Huntsville, Alabama, [2]Huntsville Hospital, Huntsville, Alabama, [3]Department of Pharmacy, Texas Children's Hospital, Houston, Texas

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is one of the most common pathogens causing pediatric infections including skin and soft tissue infections, pyogenic arthritis, osteomyelitis, and septic shock. For decades, patients were treated with antibiotics such as vancomycin and clindamycin, but there is an increasing incidence of resistance to these traditional therapies. We describe 2 cases of patients with CA-MRSA invasive infections with bacteremia who experienced vancomycin therapy failure but who were successfully treated with ceftaroline fosamil. Case 1 involves an 8-year-old Hispanic male who was diagnosed with CA-MRSA bacteremia, thigh abscess, and osteomyelitis. The patient was admitted to the pediatric intensive care unit in septic shock. Case 2 involves an 8-year-old Caucasian male who was diagnosed with CA-MRSA sepsis, right arm abscess, and osteomyelitis. We were able to successfully treat both patients with CA-MRSA sepsis and invasive infection—who failed vancomycin therapy—with ceftaroline fosamil with no adverse effects. Despite the positive outcome in both pediatric patients, clinical trials with ceftaroline fosamil are needed to further support its use in pediatric patients.

INDEX TERMS: ceftaroline fosamil, child, methicillin-resistant *Staphylococcus aureus*, osteomyelitis, pediatrics

J Pediatr Pharmacol Ther 2015;20(6):476–480

Reduced Ceftaroline Susceptibility among Invasive MRSA Infections in Children: a Clinical and Genomic Investigation

6 out of 201 invasive MRSA isolates had a ceftaroline minimum inhibitory concentration (MIC) if ≥2 μg/mL (2.9%), with two having MICs of ≥8 μg/mL (0.9%). Isolates exhibiting ceftaroline RS were all health care-associated, PVL-negative, often resistant to clindamycin, and belonging to *agr*II (Table 1). None of the subjects with a ceftaroline RS isolate experienced prior ceftaroline use.

TABLE 2 Characteristics of MRSA isolates with high MIC to ceftaroline

Subject	Strain	Diagnosis	Acquisition[a]	Hospitalization in prior 90 days	Comorbidities[e]	Ceftaroline MIC (ug/mL)	CC/ST	PBP mutations[b]	Other notable[c] mutations[b]	SCCmec	PVL	*agr* group	Clindamycin-resistant
A	TCH29587	Endocarditis	HA	Yes	Prematurity, congenital diaphragmatic hernia	2	CC5/ST5			II (2A)	Negative	II	Y
B	TCH29768	Chronic osteomyelitis	CO-HCA	No	Myelomeningocele	4	CC8/ST8		*lytD* – Y228F	IV (2B)	Negative	I	N
C	TCH30045	CLABSI	CO-HCA	Yes	CF, lung transplant	8	CC5/ST5	mecA/pbp2a – E447K		II (2A)	Negative	II	Y
D	TCH30354	CLABSI	CO-HCA	Yes	Medulloblastoma, status post autologous stem cell transplant, ventriculoperitoneal shunt	2	CC5/ST1011			II (2A)	Negative	II	Y
E	TCH32569	Endocarditis	CO-HCA	Yes	BMT	2	CC5/ST105		*mecR* (multiple)	II (2A)	Negative	II	Y
F1 (D0)	TCH32767	CLABSI[d]	CO-HCA	Yes	Prematurity, short gut	0.75	CC5/ST105		*mutL*	II (2A) VIII (4A)	Negative	II	Y
F2 (D36)	TCH32929	CLABSI	CO-HCA	Yes	Prematurity, short gut	>32	CC5/ST105			II (2A) VIII (4A)	Negative	II	Y

McNeil et al. *Antimicrob Agents Chemother* 2022;66:e0074522

Randomized Multicenter Study Comparing Safety and Efficacy of Daptomycin Versus Standard-of-care in Pediatric Patients With Staphylococcal Bacteremia

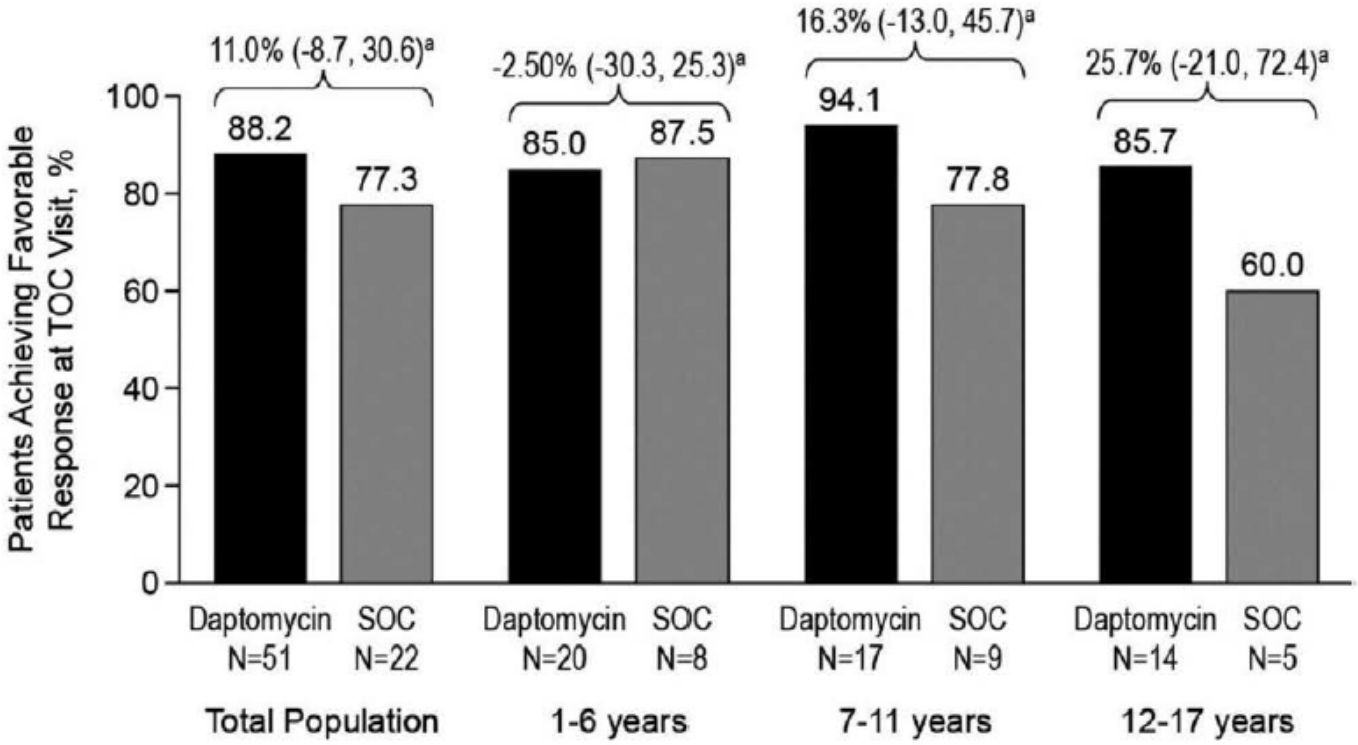


FIGURE 2. Favorable clinical response rates at the test-of-cure visit for daptomycin-treated patients and standard-of-care–treated patients by age group in the microbiologic modified intent-to-treat population. [a]Percentage difference (95% confidence interval of difference).

MRSA-Daptomycin-7, SOC-3

Daptomycin -11 osteo, 6 septic arthritis SOC-2 osteo, 4 septic arthritis

Arrieta et al. *Pediatr Infect Dis J* 2018;37:893-900

Texas Children's Hospital

BCM Baylor College of Medicine

Daptomycin for Pediatric Gram-Positive Acute Hematogenous Osteomyelitis

Results: Seventy-three patients per arm received treatment. Pathogens were isolated from 62% of patients (83% methicillin-susceptible *Staphylococcus aureus*, 9% methicillin-resistant *S. aureus* [MRSA]). Clinical improvement by Day 5 was observed in 55/71 (78%) daptomycin- and 58/70 (83%) comparator-treated MITT patients (95% confidence interval [CI]: −19.4, 7.4). This difference was not statistically significant; however, daptomycin did not meet the prespecified 15% noninferiority margin, since the lower bound of the 95% CI extended below 15%. Overall, 82% of daptomycin and 87% of comparator patients achieved clinical cure at the test-of-cure visit (secondary endpoint). More comparator patients had treatment-emergent (63% vs. 46%) and treatment-related (18% vs. 7%) adverse events.

No mention of proportion of cases with bacteremia

Bradley et al. *Pediatr Infect Dis J* 2020;39:814-823

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

X. In hospitalized children with suspected or documented AHO responding well to initial intravenous therapy and deemed ready for hospital discharge, should they be (1) be transitioned to oral therapy or (2) outpatient parenteral antibiotic therapy (OPAT)?

Recommendations:

1. For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than OPAT when an appropriate (active against the confirmed or presumed pathogen(s)) and well-tolerated oral antibiotic option is available (*strong recommendation* and *low certainty of evidence*). **Comment:** This recommendation places a high value on avoidance of harms and costs as well as on the improvement of acceptability, feasibility, and equity.

J Pediatr Infect Dis Soc 2021;10:801-844

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

Table 4. Antibiotic Choice and Duration of Therapy for *Uncomplicated* Pediatric Acute Hematogenous Osteomyelitis (AHO) Caused by *Staphylococcus aureus*[a,b]

Pathogen	Parenteral Therapy	Oral Convalescent Therapy	Duration[c]
Staphylococcus aureus, methicillin susceptible	Preferred[d]: Cefazolin Semi-synthetic penicillin[e], eg, oxacillin and nafcillin	Preferred: Cephalexin	3 to 4 weeks if uncomplicated
	Alternatives[d]: Clindamycin Vancomycin Ceftaroline	Alternative: Clindamycin	3 to 4 weeks if uncomplicated
S. aureus, methicillin-resistant, susceptible to clindamycin	Preferred: Clindamycin	Preferred: Clindamycin	3 to 4 weeks if uncomplicated
	Alternatives: Vancomycin Daptomycin Ceftaroline Linezolid	Alternatives[f]: Linezolid	No data
S. aureus, methicillin-resistant, resistant to clindamycin	Preferred: Vancomycin	Preferred: Linezolid	No data
	Alternatives: Daptomycin Ceftaroline Linezolid	Alternatives: Insufficient clinical data for the treatment of AHO to recommend other oral antibiotics with in vitro activity against *S. aureus*	No data

Cefadroxil for Completing Treatment of Osteomyelitis in Children

- 49 of 52 (94.2%) children with musculoskeletal infection (MSKI) were successfully treated with cefadroxil dosed at 30 mg/kg/day in 2 divided doses over a 10-year time period. 2 failures were associated with poor medication adherence. Weslander et al. *J Pediatr Infect Dis Soc* 2022;11:590-593

- 59 patients included in the study. There was similar occurrence of adverse effects in patients receiving cefadroxil (n=30) and cephalexin (every 6 hours; n=29), although use of cefadroxil (median daily dose 51 mg/kg/day BID) coincided with more GI adverse effects and leukopenia and use of cephalexin with more rash and neutropenia. One secondary treatment failure occurred, in a patient receiving cephalexin for treatment of septic arthritis. Hiskey et al. *Open Forum Infect Dis* 2023;10:ofad610

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

Table 4. Antibiotic Choice and Duration of Therapy for *Uncomplicated* Pediatric Acute Hematogenous Osteomyelitis (AHO) Caused by *Staphylococcus aureus*[a,b]

Pathogen	Parenteral Therapy	Oral Convalescent Therapy	Duration[c]
Staphylococcus aureus, methicillin susceptible	Preferred[d]: Cefazolin Semi-synthetic penicillin[e], eg, oxacillin and nafcillin	Preferred: Cephalexin	3 to 4 weeks if uncomplicated
	Alternatives[d]: Clindamycin Vancomycin Ceftaroline	Alternative: Clindamycin	3 to 4 weeks if uncomplicated
S. aureus, methicillin-resistant, susceptible to clindamycin	Preferred: Clindamycin	Preferred: Clindamycin	3 to 4 weeks if uncomplicated
	Alternatives: Vancomycin Daptomycin Ceftaroline Linezolid	Alternatives[f]: Linezolid	No data
S. aureus, methicillin-resistant, resistant to clindamycin	Preferred: Vancomycin	Preferred: Linezolid	No data
	Alternatives: Daptomycin Ceftaroline Linezolid	Alternatives: Insufficient clinical data for the treatment of AHO to recommend other oral antibiotics with in vitro activity against *S. aureus*	No data

J Pediatr Infect Dis Soc 2021;10:801-844

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

Table 4. Antibiotic Choice and Duration of Therapy for *Uncomplicated* Pediatric Acute Hematogenous Osteomyelitis (AHO) Caused by *Staphylococcus aureus*[a,b]

Pathogen	Parenteral Therapy	Oral Convalescent Therapy	Duration[c]
Staphylococcus aureus, methicillin susceptible	Preferred[d]: Cefazolin; Semi-synthetic penicillin[e], eg, oxacillin and nafcillin	Preferred: Cephalexin	3 to 4 weeks if uncomplicated
	Alternatives[d]: Clindamycin; Vancomycin; Ceftaroline	Alternative: Clindamycin	3 to 4 weeks if uncomplicated
S. aureus, methicillin-resistant, susceptible to clindamycin	Preferred: Clindamycin	Preferred: Clindamycin	3 to 4 weeks if uncomplicated
	Alternatives: Vancomycin; Daptomycin; Ceftaroline; Linezolid	Alternatives[f]: Linezolid	No data
S. aureus, methicillin-resistant, resistant to clindamycin	Preferred: Vancomycin	Preferred: Linezolid	No data
	Alternatives: Daptomycin; Ceftaroline; Linezolid	Alternatives: Insufficient clinical data for the treatment of AHO to recommend other oral antibiotics with in vitro activity against *S. aureus*	No data

J Pediatr Infect Dis Soc 2021;10:801-844

Trimethoprim-sulfamethoxazole Therapy for Children With Acute Osteomyelitis

- 20 children 9 months-17 years old received TMP/SMX for osteomyelitis
- 15/20 received vancomycin or clindamycin for 1-26 days (median-4.5 days)
- 8 had *S. aureus*; 5 were MRSA
- Total duration of therapy was 26-59 days (median-40 days)
- All cured; 6 had a rash

Messina et al. *Pediatr Infect Dis J* 2011

Trimethoprim–Sulfamethoxazole for Pediatric Osteoarticular Infections

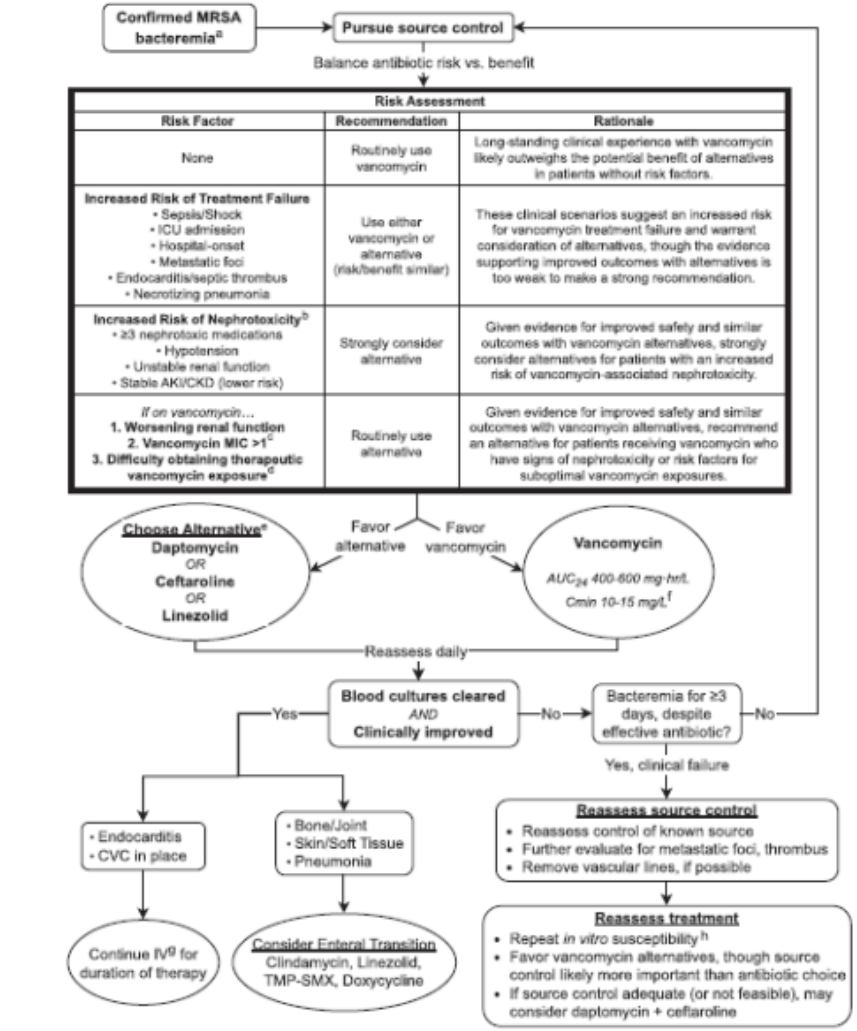
Table 3. Treatment Failure, a Composite Including Unanticipated Emergency Department (ED) or Outpatient Visits, Hospital Readmissions, Extension or Change of Antibiotic Therapy Due to Inadequate Clinical Response, or Death Within 6 Months of Discontinuing Antibiotics, in an Inverse Probability of Treatment Weighted Propensity Score Analysis of Pediatric Patients with Acute Osteoarticular Infections Treated with TMP–SMX vs. Other Antibiotic Regimens

	TMP–SMX (*n* = 25.2)	Others (*n* = 90.0)	OR (95% CI)	*P* Value
Composite outcome, *n* (%)	10.8 (43.0)	17.5 (19.4)	3.1 (0.9–10.4)	.064
Unanticipated osteomyelitis/septic joint-related ED/ outpatient visit within 6 months, *n* (%)	9.6 (37.8)	10.1 (11.2)	4.8 (1.3–17.8)	.019
Unanticipated osteomyelitis/septic joint-related hospital re-admission within 6 months, *n* (%)	2.2 (8.8)	6.3 (7.0)	1.3 (0.3–5.4)	.728
Unanticipated additional antibiotic due to lack of improvement within 6 months, *n* (%)	1.9 (7.7)	4.7 (5.2)	1.5 (0.3–7.7)	.623
Unanticipated extension of duration of antibiotics due to lack of clinical improvement within 6 months, *n* (%)	2.4 (9.5)	11.7 (13.0)	0.7 (0.2–2.6)	.592
Death within 6 months, *n* (%)	0	0		

MRSA isolated in 4 children treated with TMP-SMX vs. 7 children in the Others

McDaniel et al. *J Pediatr Infect Dis Soc* 2023;12:534-539

Time for a Change: Considering Vancomycin Alternatives for Pediatric Methicillin-Resistant *Staphylococcus aureus* Bacteremia



Haynes et al. *J Pediatr Infect Dis Soc* 2023:12:308-318

Staphylococcus aureus
Antibiotics Under Investigation in Children

- Bradley et al. Pharmacokinetics and safety of a single dose of telavancin in pediatric subjects 2-17 years of age. AAC 10/10/123
- Carrothers et al. Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Target Attainment Analyses for Dalbavancin in Pediatric Patients. PIDJ 2023 (NCT02344511 0steo study withdrawn)
- Giorgobiani et al. The Safety and Efficacy of Dalbavancin and Active Comparator in Pediatric Patients With Acute Bacterial Skin and Skin Structure Infections. PIDJ 2023
- Bosheva et al. A Phase 3, Randomized, Investigator-blinded Trial Comparing Ceftobiprole With a Standard-of-care Cephalosporin, With or Without Vancomycin, for the Treatment of Pneumonia in Pediatric Patients. PIDJ 2021
- Safety and Tolerability of Single-Dose Intravenous (IV) Oritavancin. https://clinicaltrials.gov/study/NCT05599295?cond=oritavancin%20&term=children&rank=1

Conclusions

1. Proportion of CA-*S. aureus* isolates causing invasive infections in US children that are MRSA has remained about 15-25% over the past several years, markedly decreased compared to the years CA-MRSA initially emerged.

2. Clindamycin resistance has increased among CA-*S. aureus* isolates associated with invasive infections, however, susceptibilities for TMP-SMX remain stably low.

3. Nafcillin/oxacillin/cefazolin remain the primary parenteral agents and cephalexin the primary oral agent to treat invasive MSSA infections.

4. Vancomycin and clindamycin are currently the most commonly used agents to treat invasive MRSA infections in children but this maybe changing.

Thank You

III. What is the management of MRSA bacteremia and infective endocarditis?

Bacteremia and Infective Endocarditis, Native Valve

30. Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis (**C-III**); the decision to use combination therapy should be individualized.

31. Echocardiogram is recommended in children with congenital heart disease, bacteremia more than 2–3 days in duration, or other clinical findings suggestive of endocarditis (**A-III**).

Rifampin may be useful adjunctive Rx for implant infection

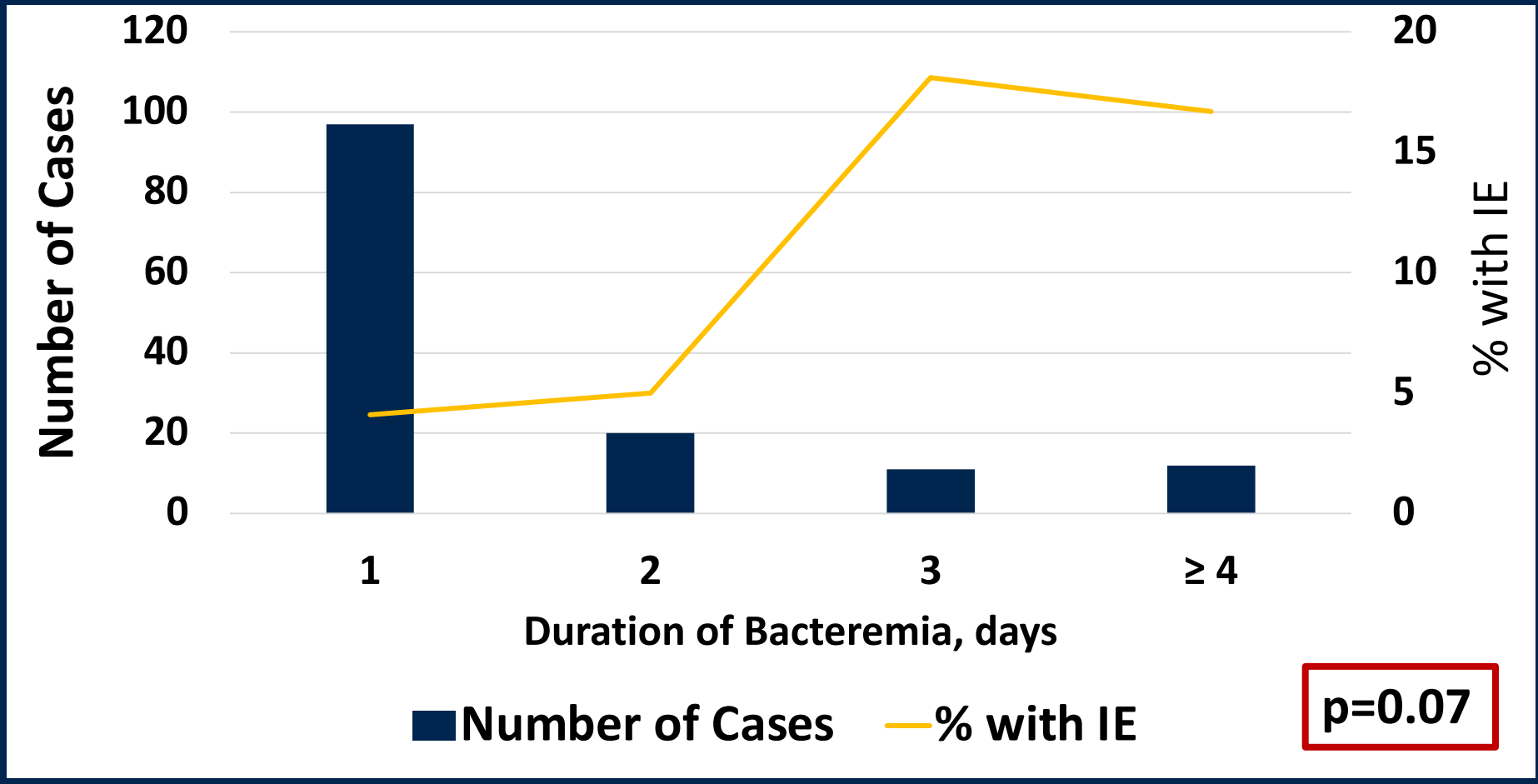
Liu et al. *Clin Infect Dis* 2011;52:285-292

Infective Endocarditis

- 140 with TTE
  - 4 with TEE (2.8%)
- 9/140 (6.4%) had findings consistent with Duke Criteria for infective endocarditis
- 1 IE patient had previously undiagnosed CHD

	Echo IE Criteria (n=9)	No Echo IE Criteria (n=131)	p-value
Age (years)	1.2 (0.6-15.5)	3.8 (0.2- 11.6)	0.76
Comorbidity	9 (100)	98 (74.8)	0.1
CHD	6 (66.7%)	27 (20.6%)	0.03
Prematurity	3 (33.3%)	30 (22.9%)	0.44
Duration SAB (days)	2 (1-3)	1 (1-2)	0.06
Prolonged Bacteremia	4 (44.4%)	19 (14.5%)	0.04
Intermittent Bacteremia	0	15 (11.4%)	0.59
CVL *in situ*	3 (33.3%)	53 (40.4%)	0.74
Days of Fever after Starting Antibiotics	2.5 (2-3)	2 (1-3)	0.64
Emboli	2 (22.2%)	5 (3.8%)	0.06

Relationship Between Duration of Bacteremia and Echo + IE



Texas Children's Hospital®

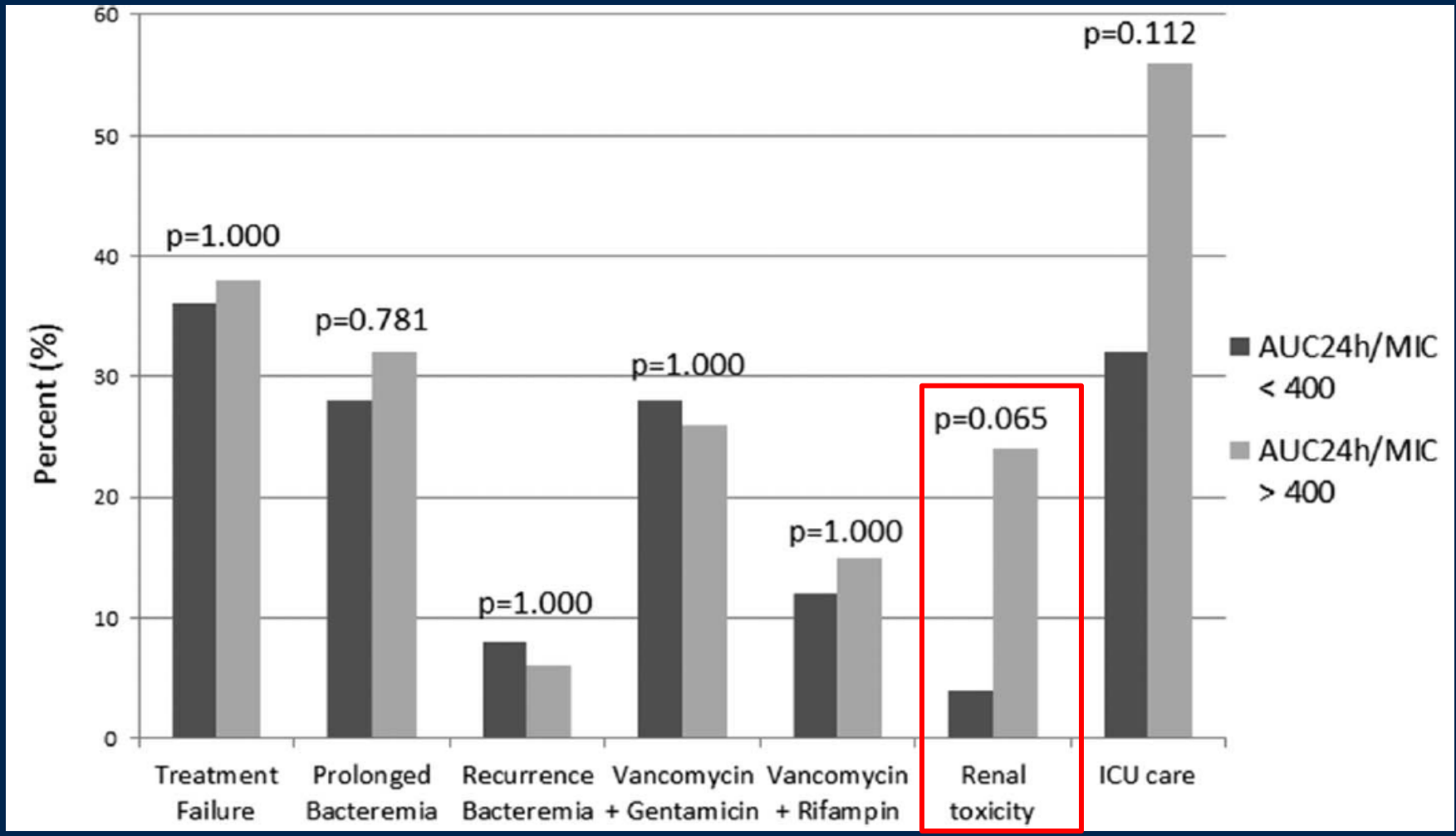
Baylor College of Medicine

Cases with Infective Endocarditis

Age, y	Comorbidities	MR/ MS	Duration of Bacteremia, days	Site of IE	Other Non-Echo Findings of IE	Other Sites	Surgical Cultures	Out-come
0.2	Premie	MS	1	TV	No	No	N/a	Cure
15.5	CHD	MS	3	PDA, PA	Pulmonary Emboli, Skin Nodules	No	N/a	Cure
1.2	TPN Dependent, Biliary Atresia	MR	4	PV	Pulmonary Emboli	No	N/a	Cure
15.6	CHD	MS	1	PV	No	No	Positive	Cure
17.8	CHD	MR	3	PV	No	No	Positive	Cure
17.4	CHD	MS	2	MV, Cardiac Abscess	Petechial Rash	No	Positive	Cure
0.8	CHD, Premie	MS	1	TV	No	No	N/a	Cure
0.07	CHD, Premie	MS	4	AV	Skin Nodules	Osteo	Negative	Cure
0.6	HLH, Hypertrophic Cardiomyopathy	MS	1	Papillary Muscle	CNS Emboli	No	N/a	Death

4/9 (44.4%) cases with IE had only a single day of SAB

Evaluation of Target Attainment of Vancomycin Area Under the Curve in Children With Methicillin-Resistant *Staphylococcus Aureus* Bacteremia



Healthcare-associated *Staphylococcus aureus* Bacteremia in Children

Evidence for Reverse Vancomycin Creep and Impact of Vancomycin Trough Values on Outcome

TABLE 2. Outcomes of *S. aureus* bacteremia (MRSA and MSSA) by Vancomycin Trough

	Trough ≤ 10 µg/mL (n = 55)	Trough 10 to ≤15 µg/mL (n = 33)	Trough > 15 µg/mL (n = 39)	*P*
Median age, mo (IQR)	15.6 (1.2–96)	2.4 (0.1–10.3)	9.4 (0.3–169.2)	0.3
Infectious diagnosis of endocarditis	7 (12.7)	10 (30.3)	4 (10.3)	0.07
Median duration of bacteremia, d (IQR)	2 (1–4)	2.5 (1–5)	2 (1–4)	0.4
Median time to resolution of fever, d (IQR)	2 (1–4)	3 (2–4)	2 (1–5)	0.2
Median length of hospital stay, d (IQR)	17.5 (10–44)	47.5 (24–104)	43.5 (25–89)	0.01
AKI	9 (16.2)	11 (33.3)	24 (61.5)	<0.001
S. aureus attributable mortality	2 (3.6)	3 (9.1)	8 (20.5)	0.02

McNeil et al. *Pediatr Infect Dis J* 2016;35:263-268

The Influence of the Route of Antibiotic Administration, Methicillin Susceptibility, Vancomycin Duration and Serum Trough Concentration on Outcomes of Pediatric *Staphylococcus aureus* Bacteremic Osteoarticular Infection

TABLE 4. Clinical Features of *S. aureus* OAI by Vancomycin Trough

	No Trough Obtained (n = 148)	Trough ≤ 10 µg/mL (n = 20)	Trough 10 to ≤15 µg/mL (n = 9)	Trough > 15 µg/mL (n = 15)	*P* Value, All Categories	*P* Value, Excluding Cases Without Trough
Age, yr	7.3 (2.4–11.6)	7.5 (4.5–12.9)	7.3 (6.8–11.9)	8.6 (1.1–13.9)	0.5	0.2
MRSA	29 (19.6)	14 (70)	7 (77.8)	8 (53.3)	<0.001	0.5
Multifocal infection	8 (5.5)	1 (5)	0	7 (46.7)	<0.001	0.001
≥2 surgical procedures	21 (14.2)	9 (45)	5 (55.6)	7 (46.7)	<0.001	0.9
Admission CRP, mg/dL	7.5 (3.8–18.6)	7.7 (5.5–24.5)	5.6 (3.8–33.1)	20.6 (15.4–27.8)	0.06	0.3
Time to 50% decline in CRP, days	7 (5–8)	8 (7–10.5)	7.5 (5.5–10.5)	7.5 (7–10)	0.1	0.7
Duration of fever, days	3 (2–6)	7 (5.5–9)	9.5 (7–15)	14.5 (6–18)	<0.001	0.5
Positive blood culture	63 (42.6)	18 (90)	7 (77.8)	14 (93.3)	<0.001	0.6
Duration of bacteremia, days	1 (1–2)	1.5 (1–3)	1 (1–2)	1 (1–2)	0.09	0.3
Length of hospital stay, days	8 (6–11.5)	11 (7.5–15.5)	13 (12–18)	22 (11–42)	<0.001	0.01
AKI	5 (3.4)	2 (10)	0	7 (46.7)	<0.001	0.01
Long-term orthopedic complications	26 (17.6)	2 (10)	3 (33.3)	4 (26.7)	0.3	0.4

McNeil et al. *Pediatr Infect Dis J* 2017;36:572-577

Epidemiology of Methicillin-Resistant *Staphylococcus aureus* Bacteremia in Children

TABLE 4 Multivariable Logistic Regression Analysis for Odds of Treatment Failure Among Children With MRSA Bacteremia (n = 174)

	OR (95% CI)	*P*
Catheter-related	0.36 (0.13–0.94)	.038
Endovascular	4.63 (0.83–25.7)	.08
Vancomycin trough <10 µg/mL	1.34 (0.49–3.66)	.56
Critical illness	2.99 (0.94–9.44)	.06
Source control intervention		
None needed	Ref	
Within 3 d	1.14 (0.47–2.8)	.77
Delayed >3 d	1.35 (0.51–3.59)	.55

Ref, reference.

Hamdy et al. *Pediatrics* 2017

Vancomycin Treatment Failure in Children With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

- Le Bonheur Children's Hospital-Memphis 2005-2015
- Treatment failures: Persistent bacteremia ≥ 7d; recurrent bacteremia within 30 d; 30 day mortality

Table 3. Correlation of Treatment Outcomes With Vancomycin Doses, Trough Concentrations, and Estimated AUC_{24}/MIC Ratios

	Treatment Success (n = 58)	Treatment Failure (n = 9)	p value
Median dose, mg/kg/day (IQR)	60 (45–60)	56 (46–80)	0.8
Median trough, mg/L (IQR)	11.8 (9.6–15.2)	13.7 (10.6–18.2)	0.24
Median AUC_{24}/MIC ratio (IQR) using the Chang[18] method*	591 (385–793)	245 (90–728)	0.07
Median AUC_{24}/MIC ratio (IQR) using the Le et al[14] method	540 (446–681)	523 (250–772)	0.6

CONCLUSIONS Treatment failure was lower than previously reported in children. AUC_{24}/MIC ratios ≥400 were frequently achieved but were not associated with treatment success, dose, or troughs. Prospective studies using standard definitions of vancomycin treatment failure are needed to understand treatment failure in children with MRSA bacteremia.

Regen et al. *J Pediatr Pharmacol Ther* 2019;24:312-319

Epidemiology of Methicillin-Resistant *Staphylococcus aureus* Bacteremia in Children

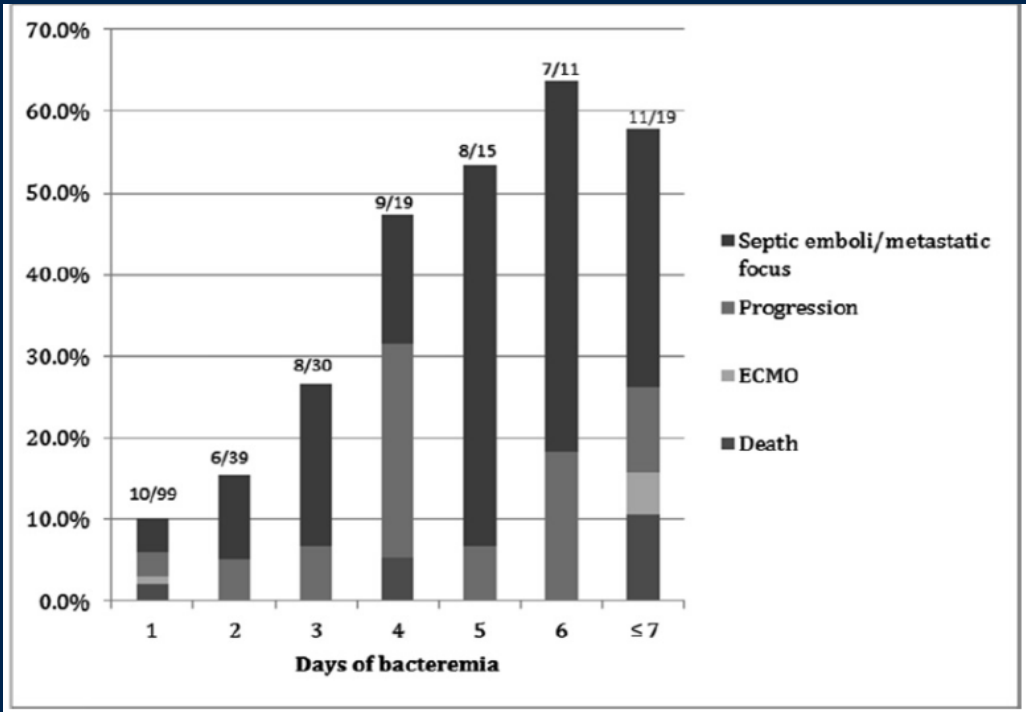


FIGURE 3
Proportion of children with complications or death, by duration of MRSA bacteremia. ECMO, extracorporeal membrane oxygenation.

For each additional day of MRSA bacteremia, the risk of developing complications increased by 50%

Hamdy et al. *Pediatrics* 2017;139:e20170183

Use of Ceftaroline Fosamil in Osteomyelitis: CAPTURE Study Experience

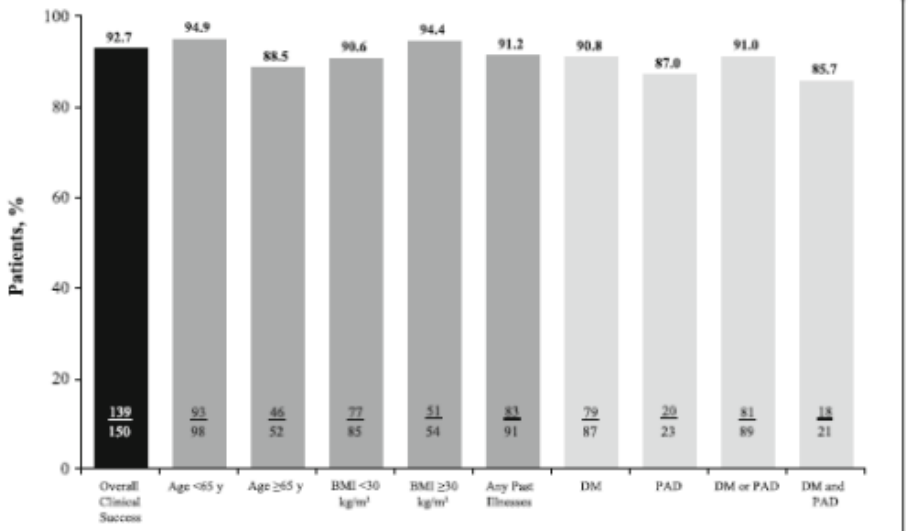


Fig. 1 Clinical success after ceftaroline fosamil therapy by relevant demographics and past illnesses*. *Patients may be in more than one category. BMI = body mass index, DM = diabetes mellitus, PAD = peripheral arterial disease

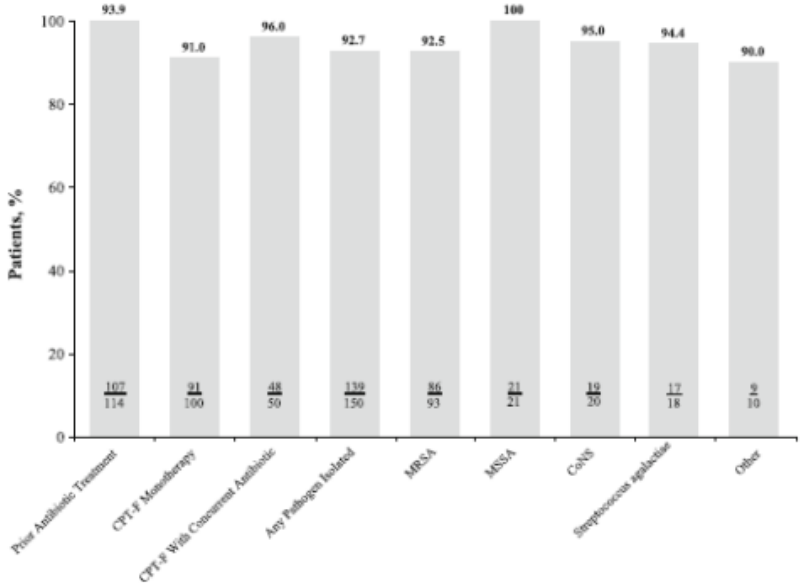


Fig. 2 Clinical success rates by antibiotic treatment and pathogen isolated*. *Patients may be in more than one category. CoNS = coagulase-negative staphylococci, CPT-F = ceftaroline fosamil, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus aureus*

Johnson et al. *BMC Infect Dis* 2019;19:183

Caveats Using Ceftaroline for Treatment of Serious MRSA Infections

- Dose in children 15 mg/kg up to 600 mg/dose infused over 2 hours every 8 hours
- Can cause neutropenia
- Encephalopathy has been described in adults with severe renal dysfunction

Vancomycin Therapeutic Drug Monitoring in Children: New Recommendations, Similar Challenges

In conclusion, based on the lack of clinical data, providers should carefully weigh the potential unknown (or even theoretical) benefits of targeting vancomycin AUC 400-800 mg*hr/L in children with the known risks of AKI associated with increasing the dose of vancomycin as well as the substantial time, effort, and costs of this process. Additional research is sorely needed on this important topic, which can hopefully provide the evidence upon which more firm guidance can be developed.