

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

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(See the Editorial Commentary by Thomsen on pages 373–4.)

Background. Coinfection with influenza virus and methicillin-resistant *Staphylococcus aureus* (MRSA) causes life-threatening necrotizing pneumonia in children. Sporadic incidence precludes evaluation of antimicrobial efficacy. We assessed the clinical characteristics and outcomes of critically ill children with influenza–MRSA pneumonia and evaluated antibiotic use.

Methods. We enrolled children (<18 years) with influenza infection and respiratory failure across 34 pediatric intensive care units 11/2008–5/2016. We compared baseline characteristics, clinical courses, and therapies in children with MRSA coinfection, non-MRSA bacterial coinfection, and no bacterial coinfection.

Results. We enrolled 170 children (127 influenza A, 43 influenza B). Children with influenza–MRSA pneumonia (N = 30, 87% previously healthy) were older than those with non-MRSA (N = 61) or no (N = 79) bacterial coinfections. Influenza–MRSA was associated with increased leukopenia, acute lung injury, vasopressor use, extracorporeal life support, and mortality than either group ($P \leq .0001$). Influenza-related mortality was 40% with MRSA compared to 4.3% without (relative risk [RR], 9.3; 95% confidence interval [CI], 3.8–22.9). Of 29/30 children with MRSA who received vancomycin within the first 24 hours of hospitalization, mortality was 12.5% (N = 2/16) if treatment also included a second anti-MRSA antibiotic compared to 69.2% (N = 9/13) with vancomycin monotherapy (RR, 5.5; 95% CI, 1.4, 21.3; $P = .003$). Vancomycin dosing did not influence initial trough levels; 78% were <10 µg/mL.

Conclusions. Influenza–MRSA coinfection is associated with high fatality in critically ill children. These data support early addition of a second anti-MRSA antibiotic to vancomycin in suspected severe cases.

Keywords. influenza; methicillin-resistant *Staphylococcus aureus*; children; vancomycin; mortality.

Epidemiologists from the Centers for Disease Control and Prevention (CDC) reported a rise in cases of influenza virus coinfection with methicillin-resistant *Staphylococcus aureus* (MRSA) in the 2006–2007 influenza season [1, 2], increasing 3-fold compared to 2004–2005 [3]. In the 2009 influenza A H1N1 pandemic (2009 pH1N1), bacterial coinfection with MRSA was an independent risk factor for influenza-related mortality in adults [4] and children [5], increasing 8-fold for

previously healthy children. Rigorous evaluation of optimal antimicrobial and other therapeutic strategies to improve the clinical outcomes of this devastating combination is impeded by its sporadic occurrence and fulminant course. Although 838 children with confirmed or suspected 2009 pH1N1 were identified across 35 US pediatric intensive care units (PICUs) in 2009, only 34 cases of MRSA coinfection were reported [5].

Intravenous vancomycin or clindamycin are recommended as the mainstay of therapy for treatment of hospitalized children with community-acquired (CA) pneumonia (CAP) if MRSA is suspected [6]. The addition of a second anti-MRSA agent is controversial [7], partly because some combinations of commonly used antibiotics for MRSA, such as linezolid with vancomycin, have shown antagonistic effects in animal models of invasive MRSA infection [8] and in experimental in vitro assays [9]. Studies in animals [10–13] and observational data

Received 8 February 2018; editorial decision 24 April 2018; accepted 8 June 2018; published online June 9, 2018.

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Clinical Infectious Diseases® 2019;68(3):365–72

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in humans [14, 15] show that *S. aureus* toxins likely are driving systemic inflammation, immune suppression, and lung necrosis. Therapies targeted at specific *S. aureus* toxins are currently being evaluated in randomized trials but are not yet clinically available. *Staphylococcus aureus* antivirulence effects have been reported in vitro for clindamycin, reducing staphylococcal protein A expression 3.5-fold [16], Panton-Valentine leukocidin expression 2.5-fold [17], and alpha hemolysin expression 2.4- to 20-fold [18] in CA-MRSA and other clinical *S. aureus* strains. Beta-lactam antibiotics were associated with increased *S. aureus* toxin expression in vitro [18, 19], and vancomycin had negligible effect.

In the absence of clinical trials, data from observational studies of real-world practice may give insights to guide therapy [20]. Therefore, in a multicenter observational study of critically ill children with confirmed influenza infection from the Pediatric Intensive Care Influenza (PICFLU) Study, we characterized the clinical presentation, immune response, and clinical outcomes of those with influenza–MRSA respiratory coinfection, comparing them to critically ill children with influenza and coinfection with non-MRSA bacteria and to those with no diagnosis of bacterial coinfection. We also aimed to examine use of antimicrobial therapy in children with influenza–MRSA coinfection and hypothesized that variability would be high and would be associated with mortality.

METHODS

Patients (aged <18 years) with confirmed CA influenza infection and respiratory failure receiving invasive mechanical ventilation admitted to a PICU that was voluntarily participating in the PICFLU Study were prospectively enrolled from December 2008 to May 2016 from 34 sites in the Pediatric Acute Lung Injury and Sepsis Investigator's Network (PALISI). Detailed methods of the PICFLU study have been reported [21–23]. We excluded patients with pre-existing lung disorders; immune compromise; mitochondrial, genetic, or neurologic disorders; and/or preexisting cardiac diseases that increase the risk of infection or respiratory failure [24]. Patients with non-subtypable influenza A were also excluded. The institutional review board at each site gave study approval, and informed consent was obtained from a parent or guardian.

Throughout the study period, sites were encouraged to follow the recommendations published by the CDC to screen all symptomatic patients admitted to the PICU for influenza and to test all intubated patients for secondary bacterial infection with Gram stain and culture of endotracheal secretions [25]. Patient management was at the clinician's discretion. The first study samples were taken as soon as possible after PICU admission, including respiratory samples from the nasopharynx and from the endotracheal tube (ETT).

Viral and Bacterial Testing and Diagnoses

Viral test results included those from the clinical site, which could have been performed prior to or after PICU admission, as well as additional study testing done at the Marshfield Clinic Research Foundation (Marshfield, WI). Influenza and other viral testing methods have been previously reported [26, 27]. Viruses tested included respiratory syncytial virus; human metapneumovirus; human rhinovirus; parainfluenza virus; influenza A and B including A subtypes H1, H3, and 2009 pH1N1; coronavirus; and adenovirus [26].

Bacterial coinfection was defined as a diagnosis at the clinical site with microbiologic identification of the pathogen within 72 hours prior to or after PICU admission (to rule out hospital-acquired infection). Cultures had to come from a sterile site (endotracheal or bronchoscopic specimen, bloodstream, or pleural fluid). Positive tests from MRSA colonization screening alone were insufficient to determine bacterial coinfection.

Definitions

Race and ethnicity were captured through a parent interview. The pediatric risk of mortality III acute physiology (PRISM III) score [28] measured severity of illness within 24 hours of PICU admission. Invasive mechanical ventilation was via an ETT. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) were acute onset of respiratory distress, hypoxia ($\text{PaO}_2/\text{FiO}_2$ ratio of ≤ 300 for ALI and ≤ 200 for ARDS), bilateral infiltrates on chest radiograph, and no evidence of left heart failure [29]. Shock requiring vasopressor support was use of a dopamine infusion >5 $\mu\text{g}/\text{kg}/\text{min}$ or any epinephrine, norepinephrine, or phenylephrine infusion to maintain blood pressure. Mortality was death during the index hospitalization.

Data and Sample Management

Site investigators collected data on baseline demographic information, illness duration, presenting symptoms, initial PICU admission findings, and selected clinical events and outcomes (hospital and at PICU discharge). Data were then entered into a REDCap electronic case report form [30] hosted on a secure server at Boston Children's Hospital. Recorded baseline values for laboratory results, vital signs, vasoactive-inotropic dosing, chest radiograph results, and oxygenation were the first recorded values in the PICU. If these values were unavailable, the values closest to admission (from transport, the emergency department, or referral hospital) were used. Data were collected as close to 08:00 as possible; data were considered missing if no values were available. Final outcome (survival/death) was tracked to initial PICU discharge date in all patients and up to hospital discharge in patients transferred to the ward.

Data on antibiotics given in the first 24 hours of PICU admission or prior to PICU admission were collected prospectively. In children with influenza–MRSA coinfection, sites collected information on timing of all antibiotics prior to and after PICU

admission as well as vancomycin trough levels, vancomycin dosing, and antibiotic susceptibility testing results retrospectively.

Samples of blood and endotracheal aspirates (if intubated) were taken at enrollment (most within 24 hours of PICU admission) and 3, 7, and 14 days later if still in the PICU. ETT aspirate was kept on ice until centrifugation; then, the ETT supernatant was aliquoted and stored at -80°C . Concentrations of cytokines were measured in duplicate by the University of Minnesota Cytokine Reference Laboratory using standard enzyme-linked immunosorbent assay as well as bead-based Luminex multiplex assays (Luminex 200 platform, Austin, TX) as described in detail in a recent publication [22].

Statistical Methods

Statistical analysis was performed using SAS software version 9.4 (Cary, NC). Categorical variables were compared using the Fisher exact test and Mann-Whitney U test. Continuous variables were analyzed using Spearman correlation and Kruskal-Wallis test with Dunn test for post-hoc analyses. Logistic regression, adjusting for age and PRISM III score, was used to confirm the association between mortality and early vancomycin monotherapy vs additional early anti-MRSA antibiotic groups.

RESULTS

We enrolled 170 children who met the inclusion and exclusion criteria across 34 sites between November 2008 and May 2016. As shown in Table 1, 30 (17.6%) were diagnosed with MRSA respiratory coinfection, 61 (35.9%) had a diagnosis of non-MRSA bacterial coinfection (31 methicillin-susceptible *S. aureus* [MSSA], 10 pneumococcus, and 20 other; see Supplementary Table 1 for details), and 79 (46.5%) had no clinical diagnosis of bacterial coinfection. All children with MRSA coinfection had 1 or more positive MRSA cultures from endotracheal aspirate, pleural fluid, and/or lung tissue, and 4 also had MRSA bacteremia.

The demographic characteristics, underlying health conditions, clinical course, and outcomes of these 3 groups of children are shown in Table 1. Children with MRSA were on average 2 times older than children in both non-MRSA groups ($P < .001$). They were more likely to be previously healthy ($P = .002$) than children with influenza alone. The children with influenza-MSSA coinfection overall had baseline characteristics and clinical outcomes similar to those with influenza who were coinfecting with non-*S. aureus* bacteria (details shown in Supplementary Table 1; all $P > .05$ except that, on average, they were older).

As depicted in Figure 1, more than 90% of children with MRSA coinfection had acute lung injury or vasopressor use for shock compared to approximately half of the non-MRSA comparison groups (all $P \leq .001$). More than 70% of MRSA patients

received extracorporeal membrane oxygenation (ECMO) support compared to less than 9% of the other groups; $P \leq .001$). Influenza-related mortality was 40% with MRSA coinfection compared to 4.3% without MRSA (relative risk [RR], 9.3; 95% confidence interval [CI], 3.8–22.9). One child with severe lung necrosis was supported on ECMO for 6 months and died soon after receiving a lung transplant. Autopsy results were available for 4 MRSA patients, 3 of whom died on ECMO support. All showed extensive areas of hemorrhagic infarction, abscess formation, necrosis, and emboli in the lung with pleural adhesions and effusions.

Death in the MRSA-coinfecting patients was associated with older age ($P = .01$) and higher PRISM III score ($P = .02$) but not with type of influenza virus infection (see Supplementary Table 2), site of MRSA culture, or bacteremia (Supplementary Table 3). Although not statistically significant ($P = .15$), of the 11 children who died, 6 (54.5%) reportedly were vaccinated against influenza that season (4 not vaccinated, 1 unavailable) compared to 3/18 (16.7%) survivors (11 not vaccinated, 4 unavailable). Time between first symptom onset and PICU admission was available from parental interview starting in the fall of 2010; for 8/11 (72.7%) children who died and 13/18 (72.2%) who survived, median days to PICU presentation was 4 (interquartile range [IQR], 3.3, 4.8) vs 2 (IQR, 2, 3), respectively ($P = .02$).

As shown in Figure 2, influenza-MRSA-coinfecting children had markedly suppressed white blood cell (WBC) counts in the first 24 hours of PICU admission compared to the non-MRSA influenza groups ($P < .0001$). The MSSA-coinfecting children had admission-day WBC values similar to those who were coinfecting with other bacteria (Supplementary Table 1). Not all children had a differential available, but profound neutropenia was common in patients with influenza-MRSA ($n = 27$; median absolute neutrophil count [ANC], 360; IQR, 120–1190; Supplementary Figure 1) compared to patients with influenza and other bacterial coinfection ($n = 51$; median ANC, 5610; IQR, 1410–10100; $P < .0001$) or influenza patients without bacterial coinfection ($n = 69$; median ANC, 8900; IQR, 4670–14710; both $P < .0001$).

Serum cytokine analysis results were available prior to 2016 (105/170 patients including 21/30 patients with MRSA). Granulocyte-colony stimulating factor (G-CSF), interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor- α were markedly elevated in the children with influenza-MRSA coinfection ($P \leq .001$; Supplementary Figure 2) compared to children with no bacterial coinfection and with other bacterial coinfection.

Antimicrobial Use and Association With Mortality

Choice of early (within the first 24 hours of PICU admission) anti-MRSA antibiotic administration in children with influenza-MRSA coinfection varied. One child who died received early clindamycin monotherapy. Early vancomycin was given to 96.7% of patients ($N = 29/30$). Figure 3 shows whether

Table 1. Characteristics and Clinical Course of 170 Children With Influenza Critical Illness With and Without Bacterial Coinfection

Characteristic/Outcome	Influenza–Methicillin-resistant <i>Staphylococcus aureus</i> (N = 30)	Influenza–Other Bacteria (N = 61)	Influenza–No Bacteria (N = 79)	P Value ^a
Male (%)	19 (63.3)	36 (59.0)	49 (62.0)	.91
Hispanic ethnicity (%)	7 (23.3)	15 (24.6)	21 (26.6)	.95
Race				.75
White (%)	25 (83.3)	44 (72.1)	55 (69.6)	.35
Black (%)	3 (10.0)	9 (14.8)	14 (17.7)	.66
Mixed/Other (%)	2 (6.7)	8 (13.1)	10 (12.7)	.74
Age, years (median, IQR)	12.7 (10.0, 14.6)	6.0 (2.2, 12.0) ^b	5.7 (2.6, 9.9) ^c	<.0001
Baseline health status ^d				
Previously healthy (%)	26 (86.7)	43 (70.5)	42 (53.2) ^e	.002
Mild chronic respiratory (%)	2 (6.7)	12 (19.7)	22 (27.6) ^f	.04
Other (%)	2 (6.7)	6 (9.8) ^g	23 (29.11) ^f	.003
Influenza type				.14
Influenza A (%)	19 (63.3)	48 (78.7)	60 (76.0)	.29
Influenza A H3N2 (%)	9 (30.0)	14 (23.0)	12 (15.2)	
Influenza A 2009 H1N1 (%)	9 (30.0)	29 (47.5)	45 (57.0)	
Influenza A Seasonal H1N1 (%)	1 (3.3)	5 (8.2)	3 (3.8)	
Influenza B (%)	11 (36.7)	13 (21.3)	19 (24.1)	.29
Received oseltamivir (%)	30 (100.0)	55 (90.2)	76 (96.2)	.11
Illness severity and outcomes				
Pediatric risk of mortality score (median, IQR)	22.0 (9.0, 28.0)	9.0 (3.0, 17.0) ^c	6.0 (3.0, 11.0) ^c	<.0001
Duration mechanical ventilation in survivors, days (median, IQR)	10.1 (5.9, 15.9)	5.1 (2.6, 9.2) ^f	5.8 (2.7, 9.3) ^e	.01
Duration pediatric intensive care unit stay, days (median, IQR)	15.6 (10.7, 28.0)	7.2 (4.7, 17.9) ^c	9.1 (5.0, 14.0) ^c	<.0001
Mortality (%)	12 (40.0)	2 (3.3) ^c	4 (5.1) ^c	<.0001

Abbreviation: IQR, interquartile range.

^aBy Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.

^b*P* < .001 compared to influenza–methicillin-resistant *Staphylococcus aureus*.

^c*P* ≤ .0001, compared to influenza–methicillin-resistant *Staphylococcus aureus*.

^dSome patients identified with more than 1 in this category.

^e*P* < .01 compared to influenza–methicillin-resistant *Staphylococcus aureus*.

^f*P* < .05.

^g*P* < .01, compared to influenza–no bacteria.

additional early anti-MRSA antibiotics were received in these 29 patients, stratifying these children by hospital survival. Although 43.3% (N = 13/29) received vancomycin monotherapy, 51.7% (N = 15/29) received additional therapies, most commonly clindamycin (4 children received a third early anti-MRSA antibiotic, 3 received ceftaroline, 1 received linezolid, and 1 received ceftaroline plus vancomycin).

Age, gender, PRISM III score, type of influenza infection, and influenza vaccination did not significantly differ between the early vancomycin monotherapy and the additional early anti-MRSA antibiotic groups (see [Supplementary Table 4](#)). Mortality was 69.2% (N = 9/13) in those who received early vancomycin monotherapy compared to 12.5% (N = 2/16) in those who received vancomycin and a second anti-MRSA agent within the first 24 hours (RR, 5.5; 95% CI 1.4, 21.3; *P* = .003); the estimated number needed to treat with more than 1 anti-MRSA agent to prevent 1 death would be 2 (95% CI, 1.2, 3.7). This finding remained significant (*P* = .01) after adjusting for illness severity in the first 24 hours (PRISM III score) and age. The majority of children who survived (11/18, 61.1%) and all 11 who died received extracorporeal life support.

For children with data available on time to presentation, 7/13 (53.8%) who received vancomycin monotherapy and 14/16 (87.5%) with additional anti-MRSA therapy reported median time between symptom onset and presentation of 4 days (IQR, 2, 5) vs 3 days (IQR, 2, 4), respectively (*P* = .18). Even with imputation of the 75th and 25th percentiles, respectively, for time to presentation for missing data (5 days for deaths and 2 days for survivors), time to presentation would not have reached statistical significance between the 2 groups (3/6 children in the vancomycin-only group with missing data were survivors).

All tested MRSA isolates were susceptible to clindamycin (N = 28, 2 MRSA isolates not tested). The minimum inhibitory concentration (MIC) of tested MRSA isolates to vancomycin was ≤1 µg/mL in 56% of the 30 children, 1–2 µg/mL in 13.3%, and not reported in 30.0%. We were able to obtain the first vancomycin trough levels from 28/29 children with MRSA who received vancomycin in the first 24 hours. We excluded 2 patients with acute renal failure on admission whose vancomycin dosing required adjustment. As shown in [Figure 4A](#), 78% of initial vancomycin trough levels were <10 µg/mL. Vancomycin dosing was not associated with vancomycin trough levels ([Figure 4B](#)).

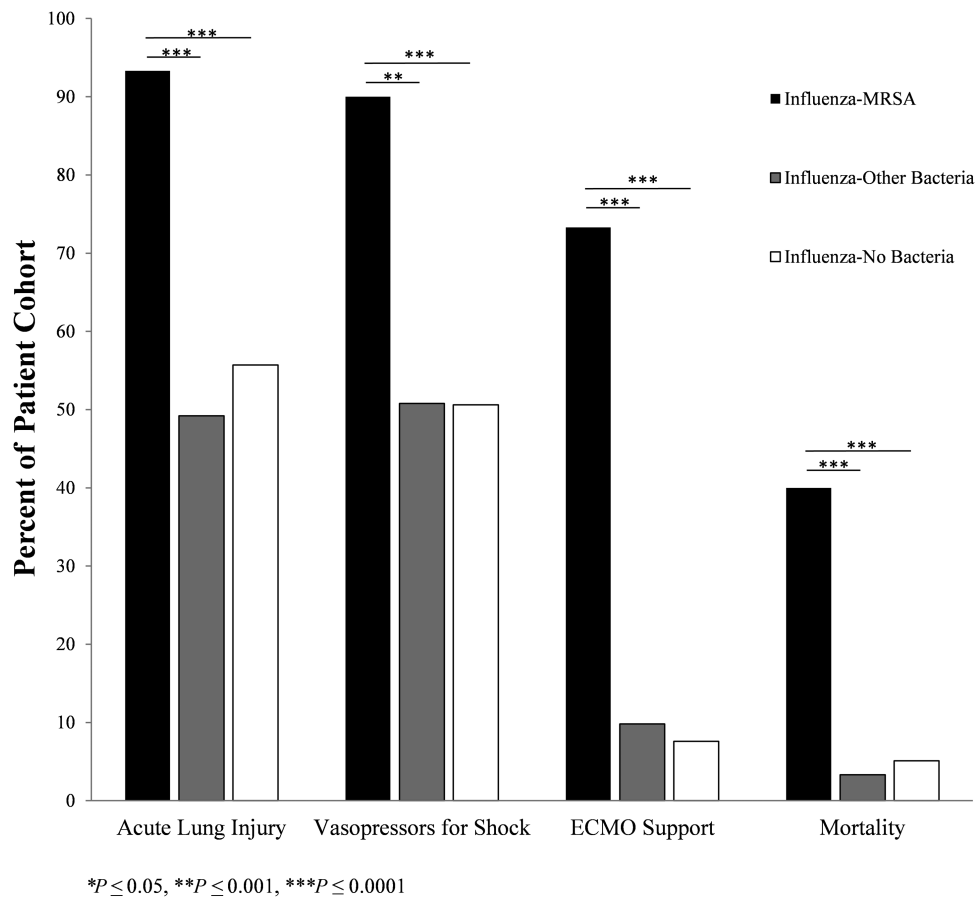


Figure 1. Clinical course and outcomes of critically ill children with influenza virus–methicillin-resistant *Staphylococcus aureus* (N = 30) compared to influenza with other bacteria identified (N = 61) and influenza with no bacteria identified (N = 79). Abbreviations: ECMO, extracorporeal membrane oxygenation; MRSA, methicillin-resistant *Staphylococcus aureus*. *P ≤ .05, **P ≤ .001, ***P < .0001. Comparisons were made using Mann-Whitney U test with the ends of the bars showing the groups compared.

DISCUSSION

Children with influenza-related acute respiratory failure in this multicenter PICU cohort who had MRSA coinfection were more severely ill than children coinfecting with other bacteria or with no bacterial coinfection and they were 9 times more likely to die. Anti-MRSA antibiotics given within 24 hours of PICU admission were associated with hospital outcomes. Children who received early vancomycin as their sole anti-MRSA agent had a 5.5 times higher risk of mortality than children who received early vancomycin plus the early addition of another anti-MRSA agent. Choice of antimicrobial therapy was mostly empiric, as bacterial diagnosis usually takes longer than 24 hours. Some factors distinguished influenza–MRSA-coinfecting children. The majority of them were in adolescence and were previously healthy. They usually developed leukopenia on their first PICU day, frequently had neutropenia (despite a higher GCSF serum level), and most often were cannulated for ECMO support. Early recognition of this patient profile could guide choice of empiric therapy.

Difficulty in reaching therapeutic levels of vancomycin in pediatric patients with good renal clearance is common [31, 32]

and not consistently improved by the addition of a vancomycin loading dose [33]. The area-under-the-curve (AUC):MIC ratio has been posited as a potentially better predictor of vancomycin efficacy than vancomycin trough levels [34, 35]. However, clinical outcomes are not reported to be improved even with adequate AUC:MIC early in invasive MRSA infections [35]. Investigators who systematically reviewed available studies concluded that vancomycin poorly penetrates lung tissue. Compared to simultaneous plasma levels, concentrations in lung epithelial lining fluid ranged from 5% to 25%, and concentrations in whole homogenized lung tissues ranged from 24% to 41% [36].

MRSA susceptibility to clindamycin, the second most commonly prescribed anti-MRSA agent, was near universal in this cohort. Unfortunately, the susceptibility of *S. aureus* to clindamycin may be declining in US children [37]. Via a mechanism of protein synthesis inhibition not present in vancomycin, clindamycin has antitoxin effects in vitro [18]. Although data from in vitro models also suggest antagonism exists when vancomycin is combined with clindamycin or linezolid [7], there is poor agreement between animal and human models of antibiotic

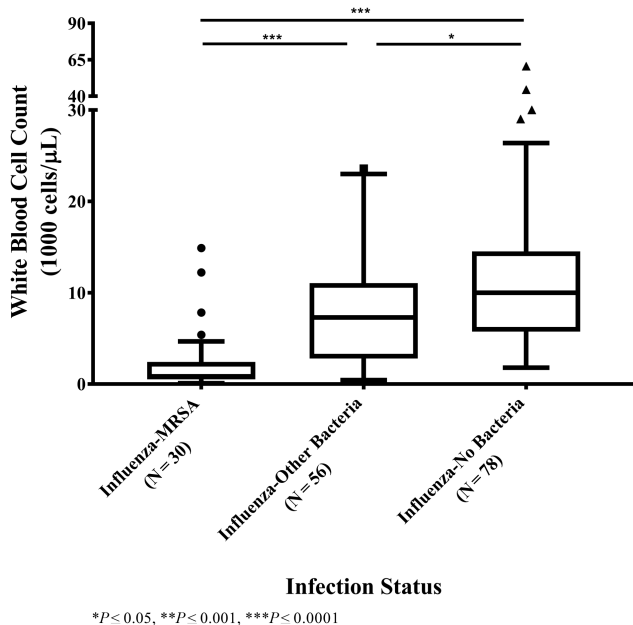


Figure 2. White blood cell (WBC) counts of children with influenza virus infection within first 24 hours of pediatric intensive care unit admission. WBC counts were available for all 30 influenza–methicillin-resistant *Staphylococcus aureus* patients, 56/61 influenza–other bacteria patients, and 78/79 influenza–no bacteria patients. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*. * $P \leq .05$, ** $P \leq .001$, *** $P < .0001$. Comparisons were made using Mann-Whitney *U* test with the ends of the bars identifying the groups compared.

antagonism or synergy when treating MRSA [38]. Ultimately, the choice of a second anti-MRSA agent should be influenced by local MRSA antibiograms [34]. Ceftaroline is clinically approved for MRSA-CAP and skin and soft tissue infections

and was used in 4 surviving patients as an adjunct antibiotic with vancomycin. Rigorous pharmacokinetic and outcome data for ceftaroline treatment in intubated children with MRSA pneumonia are lacking [39].

The strengths of this study include prospective enrollment, rigorous data collection, and sensitive influenza testing. Clinical care was not controlled, revealing high practice variability across centers in empiric choice, dosing and timing of vancomycin, and use of additional anti-MRSA antibiotics.

This study has numerous limitations. The design is observational and the cohort of MRSA patients is relatively small, including only 30 MRSA-coinfected patients and 11 MRSA-related deaths, despite involvement of 34 large PICUs for 8 years. Children with severe comorbid health conditions that predisposed them to influenza infection were excluded, limiting generalizability but decreasing potential confounding. Duration of symptoms prior to initial presentation was not available early in the study. Our analysis of the available data on time to presentation and our sensitivity analysis show that although longer time from symptom onset to PICU admission was associated with increased fatality, it was unlikely to explain the association between vancomycin monotherapy and death. We did not collect data on antimicrobial-related adverse events, which would have been difficult given the high rate of multiorgan failure on PICU admission in the MRSA-coinfected children. It is important to note that MRSA coinfection can occur with other viruses. Because our focus was on influenza virus infection, we could not determine if the clinical course and outcomes of MRSA coinfection in noninfluenza viral infection were similar.

Although limited, this “real-world evidence” [20] on antibiotic efficacy in pediatric influenza–MRSA coinfection, a

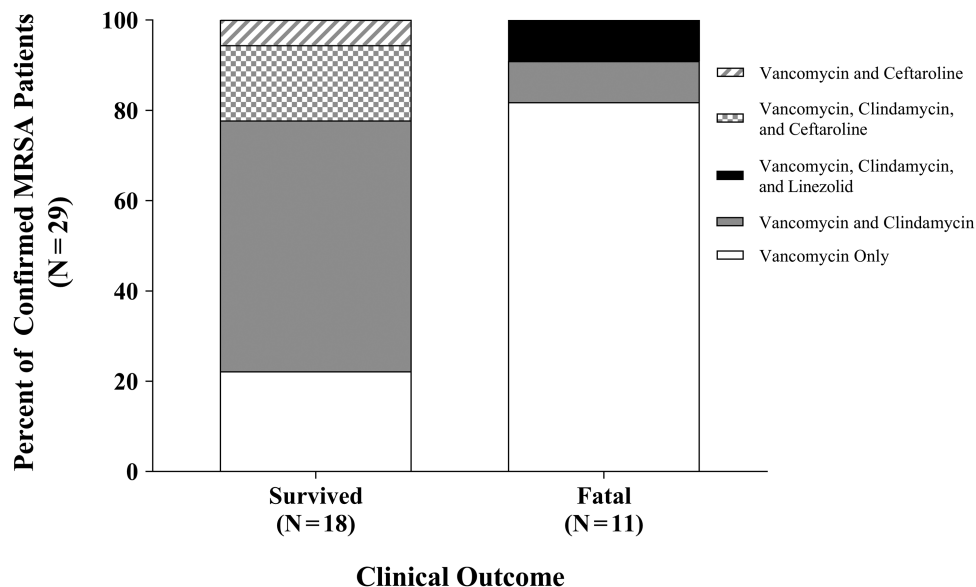
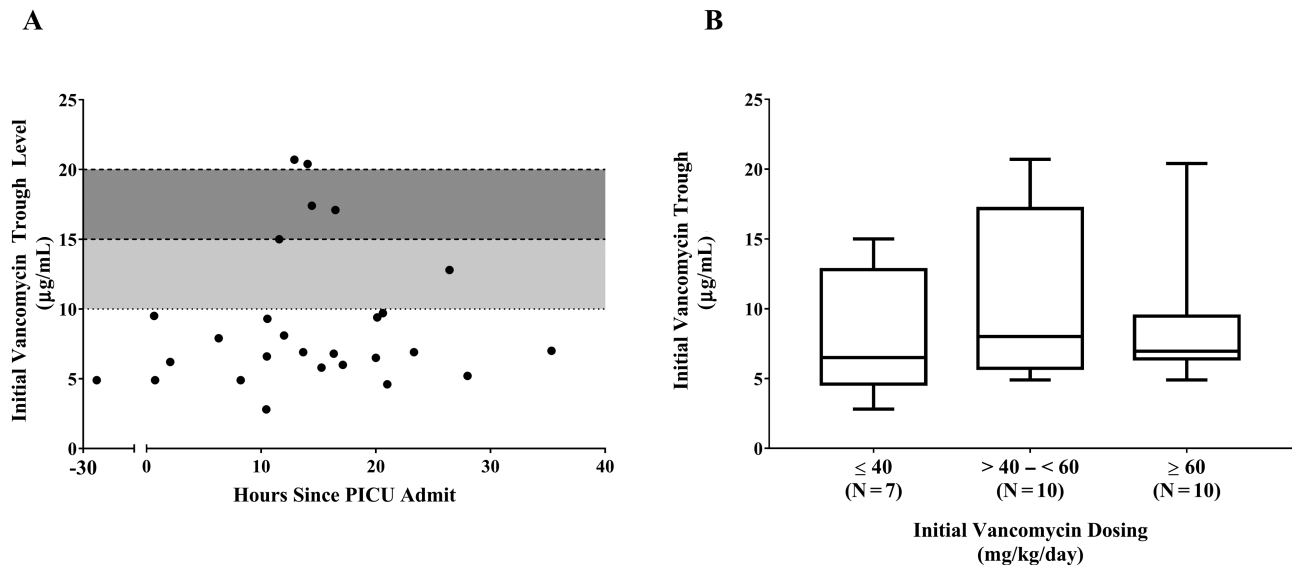


Figure 3. Comparison of vancomycin only to vancomycin with additional anti-methicillin-resistant *Staphylococcus aureus* agent(s) within the first 24 hours of pediatric intensive care unit admission stratified by survival. The relative risk (RR) of mortality in the vancomycin only group was 5.54 (95%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



2 patients were in renal failure on admission and excluded from these data.

Figure 4. (A) Initial vancomycin trough levels (prior to the fourth dose) of methicillin-resistant *Staphylococcus aureus* patients (78.5% of initial trough levels were less than 10 µg/mL). (B) Vancomycin dosing and initial trough level. Initial trough levels were not associated with initial vancomycin dose (Spearman's correlation, $P = .6$). Abbreviation: PICU, pediatric intensive care unit.

sporadic and fulminant disease with high fatality, indicates that vancomycin alone is insufficient therapy for children in the PICU with acute respiratory failure. Because results of diagnostic tests for MRSA and influenza can be delayed by more than 24 hours, empiric therapy may be needed to optimize clinical outcomes. Older age and prior good health, as well as leukopenia and shock requiring vasopressor support on presentation, were associated with MRSA coinfection. Thus, patients who present with acute respiratory distress and similar features during influenza season should prompt consideration of an additional anti-MRSA antibiotic while further diagnostic studies are pending. Although addition of clindamycin to vancomycin appears prudent in cases with high clinical suspicion of influenza-MRSA coinfection, clindamycin resistance must be monitored. A national ongoing registry of these fatal pediatric coinfections, with antimicrobial susceptibility, antibiotic management, and collection of clinical samples, could help guide care. Addition of adjunct therapies, such as antibodies targeted at *S. aureus* toxins, may decrease mortality in children with MRSA coinfection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors gratefully acknowledge the collaboration and support of PALISI PICFLU study site investigators who enrolled patients and made other major contributions to this study.

PALISI PICFLU study site investigators included the following: Michele Kong (Children's of Alabama, Birmingham); Ronald C. Sanders, Jr. and Glenda Hefley (Arkansas Children's Hospital, Little Rock); David Tellez (Phoenix Children's Hospital, AZ); Katri Typo (Diamond Children's Medical Center, Tucson, AZ); Barry Markovitz and Rica Sharon P. Morzov (Children's Hospital Los Angeles, CA); Ana Lia Graciano (Children's Hospital Central California, Madera); Natalie Cvijanovich, Heidi Flori, and Becky Brumfield (University of California-San Francisco (UCSF) Benioff Children's Hospital Oakland); Nick Anas, Adam Schwarz, and Ofelia Vargas-Shiraishi (Children's Hospital of Orange County, Orange, CA); Patrick McQuillen and Anil Sapru (UCSF Benioff Children's Hospital, San Francisco); Peter Mourani and Angela Czaja (Children's Hospital Colorado, Aurora); Christopher Carroll (Connecticut Children's Medical Center, Hartford); John S. Giuliano Jr., Joana Tala, and Lisa Palmieri (Yale-New Haven Children's Hospital, CT); Gwenn McLaughlin (Holtz Children's Hospital, Miami, FL); Matthew Paden, Keiko Tarquinio, and Cheryl L. Stone (Children's Healthcare of Atlanta at Egleston, GA); Bria M. Coates (Ann & Robert H. Lurie Children's Hospital of Chicago, IL); Neethi Pinto (University of Chicago Medicine Comer Children's Hospital, IL); Janice Sullivan and Vicki Montgomery (Norton Children's Hospital, Louisville, KY); Adrienne G. Randolph, Ruifei Xu, Anna A. Agan, Tanya Novak, and Margaret M. Newhams (Boston Children's Hospital, MA); Melania Bembea and Sapna Kudchadkar (John's Hopkins Children's Center, Baltimore, MD); Stephen C. Kurachek (Children's Hospital and Clinics of Minnesota, Minneapolis); Mary E. Hartman, Allan Doctor, and Tina Barrale (St. Louis Children's Hospital, MO); Edward J. Truemper, Sidharth Mahapatra, Mabelle Dawson, Lucinda Kustka, Kristin Malone, and Melanie Schrack (Children's Hospital of Nebraska, Omaha); Chhavi Katyal (Children's Hospital at Montefiore, Bronx, NY); Kate G. Ackerman and L. Eugene Daugherty (Golisano Children's Hospital, Rochester, NY); Steven L. Shein, Eloise Lemon, and Kathryn DeFrancesco (Rainbow Babies and Children's Hospital, Cleveland, OH); Mark W. Hall and Lisa Steele (Nationwide Children's Hospital, Columbus, OH); Neal Thomas and Debra Spear (Penn State Hershey's Children's Hospital, Hershey, PA); Scott L. Weiss, Julie Fitzgerald, Jenny L. Bush, and Kathryn Graham (Children's Hospital of Philadelphia, PA); Frederick E. Barr (Monroe Carrell Jr. Children's Hospital at Vanderbilt, Nashville, TN); Renee Higerson, and LeeAnn Christie (Dell Children's Medical Center of Central Texas, Austin); Cindy Darnell Bowens

and Marita Thompson (University of Texas Southwestern Medical Center at Dallas); Laura L. Loftis and Nancy Jaimon (Texas Children's Hospital, Houston); Douglas F. Wilson (University of Virginia Children's Hospital, Charlottesville); Rainer G. Gedeit, Kathy Murkowski, and Katherine Siegel (Children's Hospital of Wisconsin, Milwaukee); and Marc-André Dugas (Centre Hospitalier de l'Université Laval, Quebec, Canada).

Disclaimer. This work represents the findings of the authors and not necessarily the views of the National Institutes of Health (NIH) or the US Centers for Disease Control and Prevention (CDC).

Financial support. This work was supported by the NIH National Institute of Allergy and Infectious Diseases (R01AI084011 to A.G.R.) and the CDC (to A.G.R.). K.M. acknowledges support from the Boston Children's Hospital Translational Research Program and from the Charles Hood Foundation.

Potential conflicts of interest. A.R. reports consultancy fees from Bristol Myers Squibb, La Jolla Pharmaceuticals, and Genentech Inc. M.H. reports consultancy fees from Bristol Myers Squibb and grants from the NIH. S.W. reports consultancy fees from Bristol Myers Squibb, grants from the Society of Critical Care Medicine, travel accommodations from ThermoFisher Scientific, and royalties from Up-To-Date. N.T. reports consultancy fees from Therabron, Care Fusion, and Gene Fluidics. The other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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