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Concise Communication

Impact of empiric antibiotics for methicillin-resistant *Staphylococcus aureus* (MRSA) infection and associated *Clostridioides difficile* infection (CDI) risk: Secondary analysis of the CLEAR trial

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ABSTRACT

We performed secondary analyses of a postdischarge decolonization trial of MRSA carriers that reduced MRSA infection and hospitalization by 30%. Hospitalized MRSA infection was associated with 7.9 days of non-MRSA antibiotics and CDI in 3.9%. Preventing MRSA infection and associated hospitalization may reduce antibiotic use and CDI incidence.

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Methicillin-resistant *Staphylococcus aureus* continues to produce considerable morbidity, mortality, and healthcare costs.[1] Although national implementation of infection prevention measures have led to a substantial decrease in hospital-onset MRSA infections, addressing community-onset and healthcare-associated community-onset MRSA infections requires additional efforts.[1] Approximately 10% of hospitalized adult MRSA carriers (colonized or infected) experience MRSA infection in the year following discharge. Of these infections, 85% require readmission.[2] Once hospitalized, patients with MRSA infections often receive empiric antibiotics beyond focused treatment of MRSA. We aimed to quantify the extent of non-MRSA empiric antibiotics attributable to MRSA infections and assess any risk of hospital-onset CDI as a result of this treatment. These estimates can quantify the added benefit to antibiotic stewardship and CDI from prevention of MRSA infection after hospital discharge.

Methods

We conducted a secondary analysis of the CLEAR (Changing Lives to Eradicate Antibiotic Resistance) Trial that found that postdischarge decolonization (5-day regimen of mupirocin plus chlorhexidine bathing and mouthwash, repeated twice monthly for 6 months) among MRSA infected or colonized adult inpatients reduced MRSA infections by 30% in the year following discharge. The study design and patient population has been reported elsewhere.[2] We identified adult participants who were rehospitalized due to a new MRSA infection following trial enrollment between March 2011 and April 2014 to quantify antibiotics given and any hospital-onset CDI risk.

In this secondary analysis, full-text medical records with detailed medication administration records and culture reports underwent review with a standardized data collection form. Based on culture results, hospitalizations were assigned to 2 groups: (1) MRSA infection only and (2) polymicrobial infection including MRSA. We quantified the duration of oral and intravenous non-MRSA antibacterial days of therapy (DOT) given before and after culture results. Any number of doses of a specific antibiotic given in 1 calendar day was counted as 1 DOT (https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf). If a nosocomial infection occurred during MRSA hospitalization in either group, attributable antibiotics were quantified. CDI cases were determined by both CDC laboratory criteria[3] and clinical judgment of infectious diseases physicians.

Results

We identified 123 trial participants with 154 rehospitalizations due to MRSA infection that had comprehensive medication administration data (93.3% of reported trial outcomes). Of the patients included, 62 (50%) were males and the mean age was 54.1 years (standard deviation [SD], 14.7). The most common coexisting conditions included diabetes (n = 72, 59%), renal disease (n = 29, 24%), and chronic obstructive pulmonary disease (n = 25, 20%). The mean length-of-stay was 10.6 days (SD, 8.8). The most common types of MRSA infection included skin and soft-tissue infection (SSTI; n = 57, 37%), bone and joint infection (BJI; n = 30,

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Table 1. Non-MRSA Antibiotic Therapy Administered During 129 Hospitalizations for MRSA Infection[a]

Non-MRSA Antibiotics	Hospitalization due to MRSA Infection						
	MRSA-Only Infection (N=102)		Polymicrobial Infection Including MRSA (N=27)[b]		MRSA Infection, Total (N=129)		
	No. (%)	DOT (%)[c]	No. (%)	DOT (%)	No. (%)	DOT (%)	Mean DOT When Antibiotic Given
Aminoglycoside							
Gentamicin	8 (4.9)	30 (4.2)	1 (1.7)	2 (0.6)	9 (4.0)	32 (3.1)	3.6
Tobramycin	3 (1.8)	10 (1.4)	1 (1.7)	13 (4.1)	4 (1.8)	23 (2.2)	5.8
Carbapenem							
Doripenem	...	...	2 (3.3)	15 (4.8)	2 (0.9)	15 (1.5)	7.5
Ertapenem	4 (2.5)	18 (2.5)	6 (10.0)	29 (9.2)	10 (4.5)	47 (4.6)	4.7
Imipenem/Cilastatin	6 (3.7)	23 (3.2)	2 (3.3)	12 (3.8)	8 (3.6)	35 (3.4)	4.4
Meropenem	4 (2.5)	29 (4.1)	3 (5.0)	35 (11.1)	7 (3.1)	64 (6.3)	9.1
Cephalosporin							
Cefazolin	8 (4.9)	14 (2.0)	...	...	8 (3.6)	14 (1.4)	1.8
Cefepime	14 (8.6)	83 (11.7)	4 (6.7)	16 (5.1)	18 (8.1)	99 (9.7)	5.5
Ceftriaxone	19 (11.7)	57 (8.0)	4 (6.7)	12 (3.8)	23 (10.3)	69 (6.7)	3.0
Fluoroquinolone							
Ciprofloxacin	2 (1.2)	10 (1.4)	3 (5.0)	4 (1.3)	5 (2.2)	14 (1.4)	2.8
Levofloxacin	24 (14.7)	88 (12.4)	9 (15.0)	46 (14.6)	33 (14.8)	134 (13.1)	4.1
Macrolide							
Azithromycin	1 (0.6)	2 (0.3)	1 (1.7)	3 (1.0)	2 (0.9)	5 (0.5)	2.5
Monobactam							
Aztreonam	4 (2.5)	17 (2.4)	...	...	4 (1.8)	17 (1.7)	4.3
Penicillin							
Ampicillin	2 (1.2)	2 (0.3)	...	...	2 (0.9)	2 (0.2)	1.0
Amoxicillin/Clavulanate	1 (0.6)	2 (0.3)	...	...	1 (0.4)	2 (0.2)	2.0
Ampicillin/Sulbactam	1 (0.6)	6 (0.8)	2 (3.3)	6 (1.9)	3 (1.3)	12 (1.2)	4.0
Metronidazole [d]	14 (8.6)	76 (10.7)	9 (15.0)	44 (14.0)	23 (10.3)	120 (11.7)	5.2
Nitrofurantoin	2 (1.2)	8 (1.1)	...	...	2 (0.9)	8 (0.8)	4.0
Piperacillin/Tazobactam	46 (28.2)	235 (33.1)	13 (21.7)	77 (24.5)	59 (26.5)	312 (30.5)	5.3
Pre-MRSA Culture Non-MRSA DOT	...	**293 (41.3)**	...	**127 (40.4)**	...	**420 (41.0)**	...
Post-MRSA Culture Non-MRSA DOT	...	**417 (58.7)**	...	**187 (59.6)**	...	**604 (59.0)**	...
Total Non-MRSA Antibiotic DOT	163 (100)	**710 (100)**	60 (100)	**314 (100)**	223 (100)[e]	**1,024 (100)**	4.2

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; CDI, *Clostridioides difficile* infection; DOT, days of therapy.
[a]The 129 participants experiencing MRSA infection involved 48 (39%) patients randomized to the decolonization arm and 75 (61%) patients to the education arm.
[b]Polymicrobial infections most commonly involved the following non-MRSA pathogens: *Pseudomonas aeruginosa* (N=13), *Enterococcus faecium* (N=6), *Klebsiella pneumoniae* (N=6), *Escherichia coli* (N=4), and *Enterobacter cloacae* (N=3).
[c]Days of therapy (DOT) where any number of doses of a specific antibiotic given in 1 calendar day was counted as 1 DOT. The provided percentage reflects the proportion of all non-MRSA antibiotic DOT represented by that specific antibiotic.
[d]Metronidazole DOT as a treatment for CDI were excluded.
[e]The sum of hospitalizations is greater than 129 due to multiple antibiotics administered during some of the admissions.

20%), and pneumonia (n = 21, 14%). Of all hospitalized patients, 56 (36%) involved an intensive care unit stay, and 10 (7%) resulted in death, with 6 deaths (4%) attributable to MRSA infection. Across all MRSA hospitalizations, 25 (16%) involved only anti-MRSA antibiotics. Most of these hospitalizations were due to SSTI (n = 14, 56%), surgical site infection (SSI) (n = 4, 16%), and BJI (n = 3, 12%). In 18 (72%) of the 25 hospitalizations, patients had a documented history of prior MRSA infection, not just colonization.

Overall, 129 MRSA hospitalizations involved empiric antibiotic therapy targeting more than MRSA, including 66 MRSA hospitalizations (51%) involving 1 non-MRSA antibiotic agent and the remainder 63 (49%) involving 2 to 5 (mean, 2.5; SD, 0.8) non-MRSA antibiotics. MRSA cultures yielded results by a mean of hospital day 3 (SD, 1.6) and incurred a mean of 3.2 DOT (SD, 1.9) of non-MRSA antibiotics before the MRSA result and a mean of 4.7 non-MRSA DOT (SD, 5.4) afterward, for a total of 7.9 DOT

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Table 2. Description of Non-MRSA Antibiotic Therapy Administered During 6 Hospitalizations With CDI and Timing of CDI Onset

CDI Case	Type of Infection on Admission	Non-MRSA Therapy				CDI Onset, Hospital Day
		Pre-MRSA Culture, DOT	Post-MRSA Culture, DOT	Total DOT	Antibiotic Name	
Case 1	Polymicrobial[a] including MRSA	4	8	12	Ertapenem	10
Case 2	Polymicrobial[a] including MRSA	3	16	19	Piperacillin/Tazobactam, cefepime, imipenem/cilastatin	32
Case 3	MRSA only	6	2	8	Cefazolin, Piperacillin/Tazobactam	4
Case 4	MRSA only	12	0	12	Piperacillin/Tazobactam	14
Case 5	Polymicrobial[a] including MRSA	9	19	28	Cefepime, Ertapenem, Metronidazole, Meropenem, Piperacillin/Tazobactam	3
Case 6	MRSA only	4	0	4	Ceftriaxone, ampicillin	14

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; CDI, *Clostridioides difficile* infection; DOT, days of therapy.
[a]Polymicrobial infections involved the following non-MRSA pathogens: *Acinetobacter baumanii*; *Enterococcus faecium, vancomycin-resistant Enterococci, Klebsiella pneumoniae,* extended-spectrum β-lactamase–producing; *Pseudomonas aeruginosa*.

(SD, 5.8). Postculture non-MRSA antibiotic DOT exceeded preculture DOT: 59% versus 41% (Table 1). Non-MRSA antibiotics most commonly included piperacillin/tazobactam, levofloxacin, metronidazole, cefepime, and ceftriaxone (Table 1).

Across the 154 MRSA hospitalizations, 8 nosocomial infections occurred, including 6 CDIs, 1 SSI, and 1 central-line–associated bloodstream infection. The overall CDI incidence was 3.9% (95% confidence interval, 0.8–7.0), with a mean LOS of 22.2 days (SD, 12.5) compared to 10.6 days among non-CDI hospitalizations. Also, 3 CDI cases were associated with hospitalizations with MRSA-only infection, and 3 cases were associated with polymicrobial infection including MRSA. During rehospitalizations in which CDI occurred, patients had a mean of 6.3 DOT (SD, 3.5) of non-MRSA antibiotics before MRSA resulted and a mean of 7.5 DOT (SD, 8.3) afterward, for a total of 13.8 DOT (SD, 8.5). The most commonly administered agent was piperacillin/tazobactam (Table 2). CDI cases did not occur in hospitalizations involving anti-MRSA antibiotics only.

Discussion

Reduction of MRSA infection remains a national prevention priority. In recently hospitalized MRSA carriers, MRSA infection after hospital discharge is often severe enough to result in readmission. These hospitalizations due to MRSA infection were lengthy and often resulted in extensive exposure to non-MRSA antibiotics.

It has been reported that most empiric antibiotic regimens remain unchanged even after culture results were made available.[4,5] In our study, hospitalizations due to MRSA infection resulted in a week of non-MRSA antibiotics, more than half of which were given after culture results were available.

Notably, in 16% of our MRSA hospitalizations, patients received only MRSA-targeted therapy. Treating clinicians sometimes used focused anti-MRSA therapy when documentation of MRSA colonization or recent prior MRSA infection was available. When the clinical disease characteristics fit, data related to multidrug-resistant organism (MDRO) carriage and historical infection can substantially guide empiric therapy.[6]

We further demonstrated an association between hospitalized MRSA infection and hospital-onset CDI. It is well known that cocolonization with multiple MDROs and *C. difficile* occurs.[7] Our observed 3.9% hospital-onset CDI incidence during MRSA-caused hospitalizations exceeds the national incidence of acquiring CDI during a hospitalization of 0.3%[8] by 12-fold, and exceeds the other estimates of overall CDI incidence in hospitalized patients by 5-fold or greater.[9,10] Similarly, we found that commonly administered antibiotics were broad-spectrum in nature, including fluoroquinolones, cephalosporins, and β-lactamase inhibitor combinations that are known to carry a high risk for CDI.[9,10]

Our study has several limitations. First, even though its population was derived from a large clinical trial of >2,000 patients, the number of MRSA hospitalizations with complete medication administration records was <200. This low sample number limited the precision of hospital-onset CDI infection that were attributable to MRSA infection. Our reported CDI incidence may also be underestimated because we did not evaluate for postdischarge cases.

Despite these limitations, our study highlights the value of eradicating MDROs, such as MRSA, to prevent acquisition of or infection with another antibiotic-associated pathogen such as *C. difficile*. Effective prevention strategies, such as postdischarge decolonization in MRSA carriers, have been proven to prevent MRSA infections and hospitalizations in the CLEAR Trial. Therefore, these MRSA strategies will also likely reduce non-MRSA antibiotic use and CDI associated with hospitalization due to MRSA infection.

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Conflicts of interest. Raveena Singh reports conducting clinical studies in which participating nursing homes and hospitals received donated antiseptic products from Stryker (Sage Products), 3M, Clorox, Xttrium Laboratories, and Medline. James A. McKinnell reports receiving grant support and consulting fees from Achaogen and Theravance Biopharma, grant support, consulting fees, and lecture fees from Allergan, consulting fees from Cempra, Melinta Therapeutics, Menarini Group, and Thermo Fisher Scientific, and fees for serving as a research investigator from Science 37, conducting clinical studies in which participating nursing homes and hospitals received donated antiseptic products from Stryker (Sage Products), 3M, Clorox, Xttrium Laboratories and Medline, and serving as cofounder of Expert Stewardship. Loren G. Miller reports receiving grant support from Gilead Sciences, Merck, Abbott, Cepheid, Genentech, Atox Bio, and Paratek Pharmaceuticals, grant support and fees for serving on an advisory board from Achaogen and grant support, consulting fees, and fees for serving on an advisory board from Tetraphase and conducting clinical studies in which participating nursing homes and hospitals received donated

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