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. 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. Approximately 10% of hospitalized adult MRSA carriers (colonized or infected) experience MRSA infection in the year following discharge. These infections, 85% require readmission. 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. 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 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,
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.

### Table 1. Non-MRSA Antibiotic Therapy Administered During 129 Hospitalizations for MRSA Infection

| Non-MRSA Antibiotics | Hospitalization due to MRSA Infection |
|----------------------|---------------------------------------|
|                      | MRSA-Only Infection (N=102) | Polymicrobial Infection Including MRSA (N=27)
|                      | No. (%) | DOT (%) | No. (%) | DOT (%) | No. (%) | DOT (%) |
| 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
| Carbenapen           |                                      |                           |
| 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
| Fluroquinolone       |                                      |                           |
| Ciprofloxacin        | 2 (1.2) | 10 (1.4) | 3 (5.0) | 4 (1.3) | 5 (2.2) | 14 (1.4) | 2.8
| Levofoxacin          | 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) | 1,024 (100) | 4.2

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; CDI, *Clostridioides difficile* infection; DOT, days of therapy.

The 129 participants experiencing MRSA infection involved 48 (39%) patients randomized to the decolonization arm and 75 (61%) patients to the education arm.

Polymicrobial infections involving non-MRSA pathogens: *Pseudomonas aeruginosa* (N=13), *Enterococcus faecium* (N=6), *Klebsiella pneumoniae* (N=6), *Escherichia coli* (N=4), and *Enterobacter cloacae* (N=3).

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.

*Metronidazole DOT as a treatment for CDI were excluded.

The sum of hospitalizations is greater than 129 due to multiple antibiotics administered during some of the admissions.
(SD, 5.8). Postculture non-MRSA antibiotic DOT exceeded precul-
ture DOT: 59% versus 41% (Table 1). Non-MRSA antibiotics most
commonly included piperacillin/tazobactam, levofloxacin, metro-
nidazole, 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% con-
fidence 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
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 prior-
ity. 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 some-
times 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 multi-
drug-resistant organism (MDRO) carriage and historical infection
can substantially guide empiric therapy.4,5

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% 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 com-
binations that are known to carry a high risk for CDI.9,10

Our study has several limitations. First, even though its popula-
tion was derived from a large clinical trial of >2,000 patients, the
number of MRSA hospitalizations with complete medication ad-
ministration 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 under-
estimated because we did not evaluate for postdischarge cases.

Despite these limitations, our study highlights the value of eradi-
cating 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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from the University of California Irvine School of Medicine.

### Conflicts of interest

Raveena Singh reports conducting clinical studies in
which participating nursing homes and hospitals received donated antisept-
ic products from Stryker (Sage Products), 3M, Clorox, Xtrim
Laboratories, and Medline. James A. McKinnell reports receiving grant sup-
port 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 hos-
pitals received donated antiseptic products from Stryker (Sage Products),
3M, Clorox, Xtrim 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

### 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 | Pre-MRSA Culture, DOT | Post-MRSA Culture, DOT | Total DOT | Antibiotic Name | CDI Onset, Hospital Day |
|----------|--------------------------------|-----------------------|------------------------|-----------|----------------|------------------------|
| Case 1   | Polymicrobial including MRSA   | 4                     | 8                      | 12        | Ertapenem       | 10                     |
| Case 2   | Polymicrobial including MRSA   | 3                     | 16                     | 19        | Piperacillin/Tazobactam, cefepime, imipenem/clastatin | 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 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.

*Polymicrobial infections involved the following non-MRSA pathogens: Acinetobacter baumannii, Enterococcus faecium, vancomycin-resistant Enterococci; Klebsiella pneumoniae, extended-spectrum β-lactamase–producing; Pseudomonas aeruginosa.
antiseptic products from Stryker (Sage Products), 3M, Clorox, Xtrarium Laboratories, and Medline. Susan S. Huang reports conducting clinical studies in which participating nursing homes and hospitals received donated antiseptic products from Stryker (Sage Products), Molnycke, 3M, Clorox, Xtrarium Laboratories, and Medline. All other authors report no conflicts of interest relevant to this article.

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