GRAM POSITIVES: *Staphylococcus aureus* and Vancomycin-resistant Enterococci

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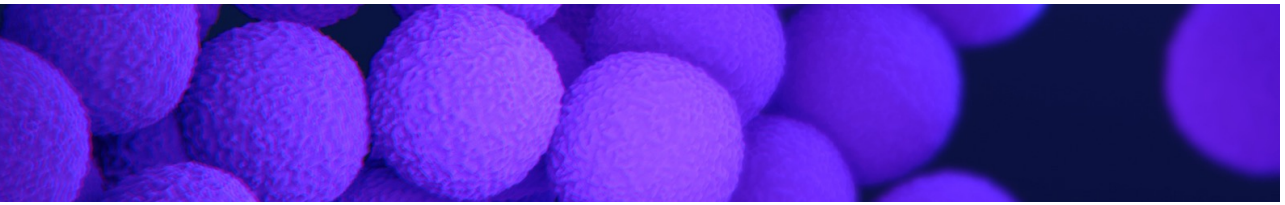
Drug Development Considerations for the Prevention of HealthCare-Associated Infections—
Virtual Public Workshop

August 30, 2022

No Financial Disclosures

The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention

What We Need



Staphylococcus aureus

- More robust decolonization and pathogen reduction regimens for a broad collection of healthcare settings
- Data on the effectiveness of other decolonization and pathogen reduction agents
    - Microbiome sparing, limited side effects, limited resistance

Vancomycin-resistant Enterococci (VRE)

- Effective decolonization and pathogen reduction regimens
    - Need for larger clinical trials and novel approaches

THE PROBLEM

Staphylococcus aureus Background

- **Gram-positive bacteria**
  - Common cause of infections in the community and healthcare including skin and soft-tissue, pneumonia, and bloodstream infections (BSIs)
  - Methicillin-susceptible *S. aureus* (MSSA)
  - Methicillin-resistant *S. aureus* (MRSA)
    - Resistant to many commonly used first-line antibiotics
    - Transmission of a clonal strain (USA300) in community settings led to large increases in infections among individuals without healthcare-related risk factors in the United States
- **Healthcare-associated infections (HAIs)**
  - Most common pathogen for surgical site infections (SSIs) reported to the National Healthcare Safety Network (NHSN)[1]
  - Second most common pathogen causing HAIs in hospitals[2]

1) Weiner-Lastinger LM, et al, ICHE 2020;41(1):1-18
2) Magill SS, et al. NEJM 2018;379:1732-1744

Staphylococcus aureus: MRSA National Estimates

In 2020, an estimated 279,300 MRSA infections occurred among hospitalized patients in the United States[1]

Impact of COVID-19: National hospital-onset MRSA bacteremia estimates in 2020 compared to respective 2019 quarters[2]

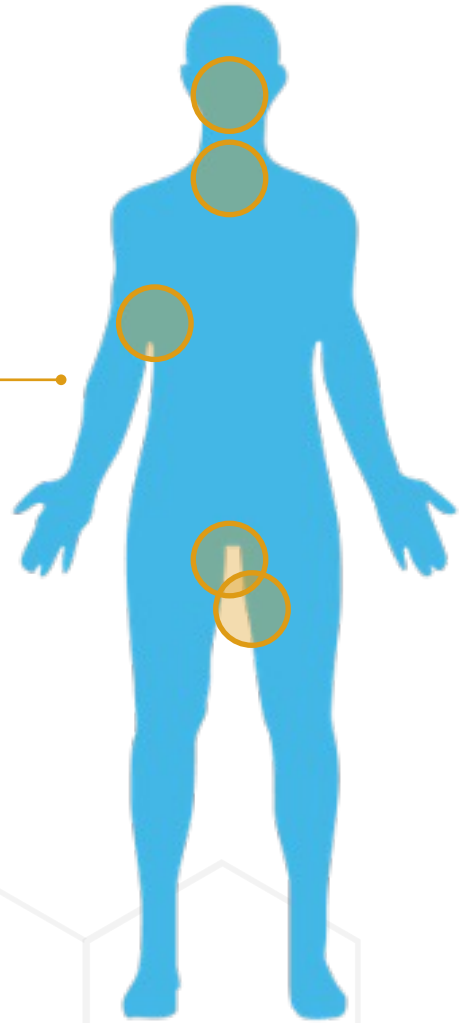
	2020 Q1	2020 Q2	2020 Q3	2020 Q4
CLABSI	↓ −11.8%	↑ 27.9%	↑ 46.4%	↑ 47.0%
CAUTI	↓ −21.3%	No Change[1]	↑ 12.7%	↑ 18.8%
VAE	↑ 11.3%	↑ 33.7%	↑ 29.0%	↑ 44.8%
SSI: Colon surgery	↓ −9.1%	No Change[1]	↓ −6.9%	↓ −8.3%
SSI: Abdominal hysterectomy	↓ −16.0%	No Change[1]	No Change[1]	↓ −13.1%
Laboratory-identified MRSA bacteremia	↓ −7.2%	↑ 12.2%	↑ 22.5%	↑ 33.8%
Laboratory-identified CDI	↓ −17.5%	↓ −10.3%	↓ −8.8%	↓ −5.5%

1) CDC 2022 COVID-19 U.S. Impact on Antimicrobial Resistance
https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf
2) Weiner-Lastinger LM, et al, ICHE 2022;43(1):12-25

Staphylococcus aureus Background

- **Spread by contact with infected or colonized individuals or contaminated surfaces, often via contaminated hands**

- **Colonization**
  - Nares, axilla, groin, perineum, pharynx
  - 1/3 of population colonized with *S. aureus;* ~1% with MRSA
  - Duration ranges from weeks to years for MRSA (median 88 weeks)[1]
  - Groups at higher risk for MRSA colonization:
    - Long-term care facility residents,
    - Healthcare personnel,
    - Individuals with extensive healthcare exposure and/or antibiotic receipt
  - Among hospitalized patients newly colonized with MRSA ~15% progress to clinical infection[2]



1) Shenoy ES, et al. BMC Infect Dis 2014; 14: 177
2) Balm MN, et al. BMC Infect Dis 2013; 13:491

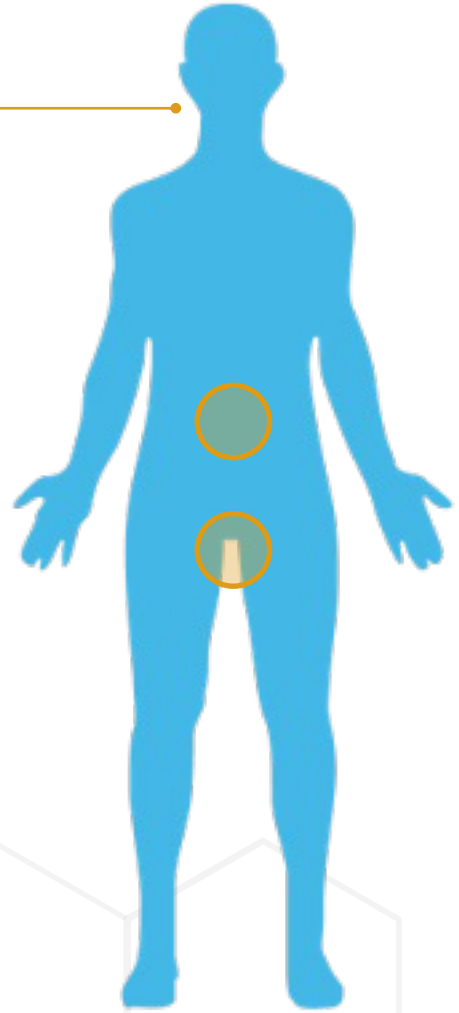
Vancomycin-resistant Enterococci (VRE) Background

- **Gram-positive bacteria**
  - Endemic in the United States
  - Increasingly resistant to additional existing antibiotics, raising concern that the remaining drugs to treat VRE may become less effective[1]
- **Common cause of HAIs including BSIs, SSIs, and urinary tract infections**
  - In 2020, an estimated 50,300 VRE infections occurred among hospitalized patients in the United States[2]
- **Spread by direct contact with infected or colonized individuals or contaminated surfaces, often via contaminated hands**
  - Environmental contamination

1) CDC 2019 Antibiotic Resistance Threat Report
https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
2) CDC 2022 COVID-19 U.S. Impact on Antimicrobial Resistance
https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf

Vancomycin-resistant Enterococci (VRE) Background

- **Colonization**
  - GI tract and occasionally the urinary tract (similar to carbapenem-resistant Enterobacterales)
  - Rates of colonization among U.S. patients admitted to intensive care units (ICU) is 12.3%[1]
  - Duration ranges from weeks to years (median 26 weeks)[2]
  - Risk factors for colonization include prolonged healthcare exposures, invasive devices, antibiotic receipt, and long-term care residence
  - Progression from colonization to infection
    - Colonization among cancer patients is ~20%; 1/8 go on to develop bloodstream infections[3]
    - Intestinal VRE domination increases risk of bloodstream infection 9-fold risk among hematopoietic stem cell transplantation patients[4]
    - Progression to infection among colonized ICU patients varies widely from 0% to 45%[1]



1) Ziakas PD, et al. PLOS ONE 2013; 8 (9): e75658
2) Shenoy ES, et al. BMC Infect Dis 2014; 14: 177
3) Alevizakos, M et al. Open Forum Infect Dis 2016; 4 (1): ofw246
4) Taur, Y, et al. Clinical Infectious Diseases 2012; 55(7): 905-914

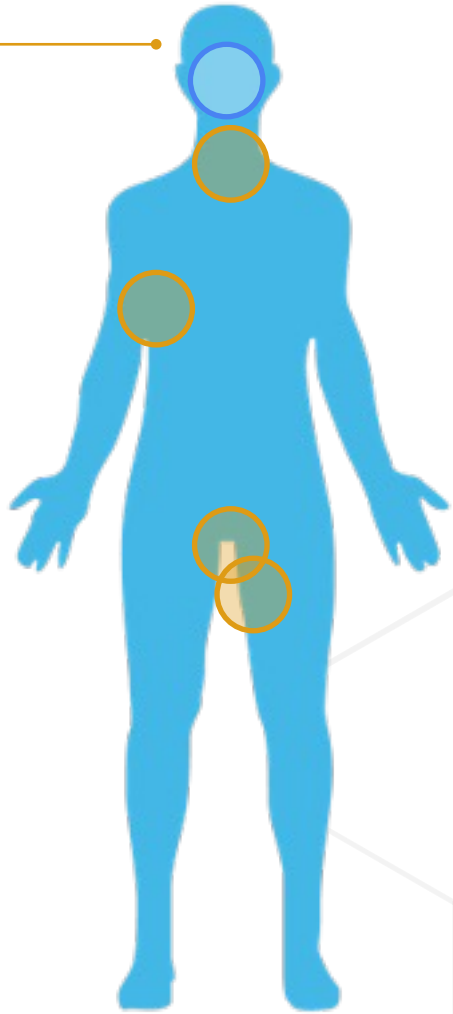
WHAT WE HAVE

Current tools, studies, and data gaps

MRSA Decolonization and Pathogen Reduction

- **Intranasal antistaphylococcal agent + topical antiseptic**
  - Intranasal agent options
    - Mupirocin (antibiotic)
      - Most evidence to support efficacy
      - Resistance can occur
    - Iodophor (antiseptic)
    - Alcohol-based agents (antiseptic)

- **Topical antiseptic: Chlorhexidine Gluconate (CHG)**
  - Common regimen for *S. aureus*
    - Intranasal mupirocin twice a day to each nare for 5 days + topical CHG wash or wipes daily for 5 days



MRSA Decolonization and Pathogen Reduction: REDUCE MRSA Trial[1]

- "REDUCE:" Cluster randomized 43 hospitals (74 adult ICUs):

Arm 1: Routine Care	Arm 2: Targeted Decolonization	Arm 3: Universal Decolonization
▪ Screened patients on ICU admission ▪ Isolated MRSA+	▪ Screened patients on ICU admission ▪ Isolated MRSA+ ▪ Decolonized if MRSA+ (5 days mupirocin, 5 days CHG)	▪ No screening ▪ Isolated known MRSA+ ▪ Decolonized all (5 days mupirocin, daily CHG)

- Outcomes: MRSA clinical cultures, MRSA BSIs, all cause BSIs
- 74,256 patients; 282,803 ICU patient-days


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2013 VOL. 368 NO. 24

Targeted versus Universal Decolonization to Prevent ICU Infection

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1) Huang SS, et al. NEJM 2013; 368 (24):2255-2265

MRSA Decolonization and Pathogen Reduction: REDUCE MRSA Trial (continued)[1]

- "REDUCE:" Cluster randomized 43 hospitals (74 adult ICUs):

Arm 1: Routine Care	Arm 2: Targeted Decolonization	Arm 3: Universal Decolonization
▪ Screened patients on ICU admission ▪ Isolated MRSA+	▪ Screened patients on ICU admission ▪ Isolated MRSA+ ▪ Decolonized if MRSA+ (5 days mupirocin, 5 days CHG)	▪ No screening ▪ Isolated known MRSA+ ▪ Decolonized all (5 days mupirocin, daily CHG)

"REDUCE" RESULTS (relative to baseline)

8% reduction in MRSA clinical cultures; 1% reduction in BSIs (all cause)	25%* reduction in MRSA clinical cultures; 22%* reduction in BSIs (all cause)	37%* reduction in MRSA clinical cultures; 44%* reduction in BSIs (all cause)

Universal decolonization resulted in significantly greater reductions in the rate of all BSIs than either targeted decolonization or routine care

*Indicates statistically significant reduction

1) Huang SS, et al. NEJM 2013; 368 (24):2255-2265

S. aureus Decolonization and Pathogen Reduction: Other Settings

Study	Population	Design	Intervention	Results
ABATE Infection Trial[1]	Hospitalized patients outside the ICU	Cluster randomized trial	Universal daily CHG bathing + Mupirocin for MRSA carriers	30%* greater reduction in MRSA clinical cultures among those with indwelling devices
Project CLEAR1[2]	MRSA carriers at hospital discharge	Randomized controlled trial (RCT)	CHG bathing for 5 days + mupirocin for five days, twice a month for 6 months	30%* reduction in risk of MRSA infection
Protect[3]	Nursing home residents	Cluster randomized trial	Universal daily CHG bathing + 5 days iodophor (every other week)	32%* greater reduction in hospital transfer due to infection
Bode et al.[4]	Hospitalized patients (primarily surgical)	RCT	Screening + CHG and mupirocin for *S. aureus* carriers	58%* reduction in *S. aureus* infections

*Indicates statistically significant reduction

1) Huang SS, et al. Lancet 2019; 393 (10177):1205-1215
2) Huang SS, et al. NEJM 2019; 380 (7):638-650
3) Miller et al. ID week abstract 2021. Data are preliminary
4) Bode et al. NEJM 2010; 362 (1): 9-17

S. aureus Decolonization and Pathogen Reduction: Other Settings (continued)

Study	Population	Design	Intervention	Results
MARS Study[1]	Surgical patients	RCT	mupirocin	51%* reduction in nosocomial *S. aureus* infections among carriers
STOP SSI[2]	Surgical patients	Quasi-experimental before-and-after	Screening + CHG and mupirocin for *S. aureus* carriers	42%* reduction in complex *S. aureus* SSIs
Ristagno et al.[3]	Neonatal ICU (NICU) patients	Single center quasi-experimental before-and-after	Universal mupirocin for five days every 5 weeks	73%* reduction in invasive *S. aureus* infections

- **Decolonization and Pathogen Reduction for MRSA has proven successful**
  - Resulted in recommendations from CDC and the Society for Healthcare Epidemiology of America (SHEA)
  - Widely implemented: 63% of U.S. hospitals routinely provide CHG bathing; 37% routinely use CHG + an intranasal antistaphylococcal agent[4]

*Indicates statistically significant reduction

1) Perl et al. NEJM 2002; 346 (24): 1871-1877
2) Schweizer et al. JAMA 2015; 313 (21): 2162-2171
3) Ristagno et al. ICHE 2018; 39(6):741-745
4) Unpublished internal data from hospitals responding to NHSN Annual Survey, 2021: The findings and conclusions herein are draft and have not been formally disseminated by CDC and should not be construed to represent any agency determination or policy. Data are preliminary.

VRE Decolonization and Pathogen Reduction

- No approved products for VRE decolonization
  - Use of CHG for pathogen reduction can reduce transmission and infection: 67% greater reduction in VRE clinical cultures among patients with indwelling devices[1]

- Multiple decolonization and pathogen reduction approaches investigated
  - Antibiotics
  - Other drugs with activity against VRE
  - Gut microbiome-modifying therapies
  - Combination approaches

- Generally small case series or trials with mixed results, limited follow up, and colonization rebound

1) Huang SS, et al. Lancet 2019; 393 (10177):1205-1215

VRE Decolonization and Pathogen Reduction: Antibiotics & Other Drugs

- **Antibiotics**
  - Resistance, poor tolerance, gut microbiome disruption
  - Oral Bacitracin
    - Review of literature identified 76 patients undergoing decolonization with bacitracin[1]
      - VRE clearance 43%-100%; only 33%-53% at 3 weeks
  - Ramoplanin RCT: 68 participants[2]
    - 85% VRE clearance at day 7 in treatment arms vs. 0% in placebo; no significant difference at day 21

- **Ebselen: Synthetic organoselenium compound[3]**
  - Potent in vitro activity against Enterococcus
  - In mouse model reduced VRE fecal burden by 99%

1) Cheng VC, et al. BMC Infectious Diseases 2014; 14:514
2) Wong MT, et al. CID 2001; 33 (9): 1476-82
3) AbdelKhalek A, et al. PLOS One 2018; 13 (6):e0199710

VRE Decolonization and Pathogen Reduction: Gut Microbiome-Modifying Therapies

- **Probiotics**
  - Certain commensal bacteria inhibit VRE growth such as *Barnesiella spp*.[1]
    - Prevent intestinal domination
  - Currently 20 studies that have or are evaluating probiotics for multidrug-resistant organism (MDRO) decolonizaiton[2]
    - Mixed results: 10 showed no effect
    - VRE RCT using oral *Lactobacillus rhamnosus* GG[3]: 11/11 (100%) in treatment arm had VRE clearance at 4 weeks versus 1/12 (8%) in control arm

- **Fecal Microbiota Transplantation (FMT)**
  - Multiple studies mostly case series; mixed results
  - FMT to decolonize VRE carriers during a hospital outbreak in France[4]
    - 7/8 (87.5%) decolonized three months after therapy

1) Ubeda C, et al. Infection and Immunity 2013; 81 (3): 965-973
2) Feehan A, et al. Microorganisms 2020; 8(2):166
3) Manley KJ, et al. Med J Aust 2007; 186(9): 454-457
4) Davido B, et al. Med Mal Infect 2019; 49 (3): 214-218

WHAT WE NEED

S. aureus Future Directions

- **Decolonization and pathogen reduction for MRSA carriers has proven successful**
  - Several large trials have demonstrated significant reductions in infections among different populations
  - Resulted in recommendations from CDC and the Society for Healthcare Epidemiology of America (SHEA)
  - Universal approaches for high-risk patients during high-risk periods can reduce MSSA infections
- **Need for more robust MRSA decolonization and pathogen reduction regimens in additional settings**
  - E.g., long-term care facilities, outpatient dialysis, burn units, post-discharge decolonization, etc.
- **Data on the effectiveness of other decolonization pathogen reduction agents for *S. aureus***
  - Microbiome sparing, limited side effects, limited resistance
  - Novel approaches: bacteriocins (lysostaphin), phage therapy, monoclonal antibody neutralizing staphylococcal protein A, etc.

VRE Future Directions

- **Studies assessing VRE decolonization and pathogen reduction strategies have shown mixed results**
  - Several approaches have or are currently being investigated
  - At least 3 ongoing trials evaluating FMT for VRE decolonization listed on clinicaltrials.gov
  - Need for larger clinical trials and novel approaches
  - Potential for large impact on VRE infections

Thank you

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For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Read more about Pathogen Reduction & Decolonization | CDC

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