Infection Control & Hospital Epidemiology (2023), **44**, 315–318
doi:10.1017/ice.2021.482

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Concise Communication

Post-discharge decolonization of patients harboring methicillin-resistant *Staphylococcus aureus* (MRSA) USA300 strains: secondary analysis of the CLEAR Trial

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Abstract

The CLEAR Trial recently found that decolonization reduced infections and hospitalizations in MRSA carriers in the year following hospital discharge. In this secondary analysis, we explored whether decolonization had a similar benefit in the subgroup of trial participants who harbored USA300, using two different definitions for the USA300 strain-type.

(Received 10 August 2021; accepted 12 November 2021; electronically published 16 December 2021)

Introduction

Despite a substantial decline in methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections between 2005-2012, recent progress has slowed and MRSA remains a major cause of morbidity and mortality in the U.S.[1] MRSA was primarily healthcare-associated until the mid-1990s, when a specific clone began appearing in the community with distinctive antimicrobial susceptibility patterns and epidemiologic features, including a propensity for causing necrotizing infection.[2] USA300 is the predominant community-associated MRSA strain in the U.S., and has emerged as a significant cause of healthcare-associated infection.[3,4]

There has been longstanding interest to examine novel strategies to prevent infections due to USA300. It is unclear whether USA300 prevention requires unique strategies compared to other strains (e.g., USA100) because of differences in virulence genes and clinical presentation.[1–4] Research to identify the most effective strategies for preventing USA300 is warranted because evidence suggests that bloodstream infections from USA100 have declined while those due to USA300 have not.[1,3]

Risk for invasive MRSA infection is greatest in the first six months following hospital discharge and remains elevated for one year.[5] The CLEAR (Changing Lives by Eradicating Antibiotic Resistance) Trial found that decolonization reduced MRSA infection by 30% and all-cause infection by 17% among recently hospitalized MRSA carriers in the year post-discharge.[6] It is possible that response to decolonization differs when comparing USA300 to other MRSA strain-types. We conducted a secondary analysis of the CLEAR Trial to evaluate whether decolonization had a similar benefit among USA300 carriers as it did for the full trial population.

Methods

CLEAR was a randomized controlled trial of 2,121 recently hospitalized MRSA carriers from January 2011–January 2014.[6] Consented participants were randomized to hygiene education alone or hygiene education plus repeated decolonization consisting of a 5-day regimen of 4% chlorhexidine soap and 0.12% chlorhexidine mouth rinse plus twice-monthly nasal mupirocin for 6 months post-discharge. Nares, skin, throat, and, wounds, if present, were swabbed upon enrollment and at 1, 3, 6, and 9 months of follow-up. This trial was approved by the University of California, Irvine institutional review board.

MRSA strains from participants who completed all follow-up visits were processed for whole genome sequencing (WGS).[7] Sequencing reads were assembled de novo using SPAdes v3.12.09. Contigs <500bp were discarded. The *in silico* multi-locus sequence typing (MLST) was inferred from assemblies using PUBMLST database (https://pubmlst.org/saureus/) and custom scripts. Staphylococcal cassette chromosome *mec* (SCC*mec*) typing was performed using pairwise blast to SCC*mec* elements (*ccr*, *mec*A, *mec*I, *mec*R genes). Combination and orientation of SCC*mec* hits were parsed by custom scripts to infer SCC*mec* type as defined in (http://www.sccmec.org). Staphylococcal protein A (*spa*) typing was performed using Ridom database (http://www.spaserver.ridom.de). Panton-Valentine Leukocidin (PVL) LukS/LukF genes and the arginine catabolic mobile element (ACME-arcA) were assessed for descriptive purposes.

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Cite this article: Gussin GM, *et al.* (2023). Post-discharge decolonization of patients harboring methicillin-resistant *Staphylococcus aureus* (MRSA) USA300 strains: secondary analysis of the CLEAR Trial. *Infection Control & Hospital Epidemiology*, 44: 315–318, https://doi.org/10.1017/ice.2021.482

Table 1. Characteristics of USA300 Carriers in the Project CLEAR Trial

Characteristic	USA300 2-Criteria Definition MLST 8, SCC*mec* type IV (N = 420)			USA300 3-Criteria Definition MLST 8, SCC*mec* type IV, *spa* t008 (N = 321)		
	Education N (%)	Decolonization N (%)	P-value	Education N (%)	Decolonization N (%)	P-value
N	207	213		165	156	
Age (Mean (SD))	55.0 (16.2)	54.7 (14.5)	0.85	54.8 (16.2)	54.5 (14.5)	0.86
Male	91 (44.0)	86 (40.4)	0.49	92 (55.8)	93 (59.6)	0.50
Coexisting conditions[a]						
Diabetes	83 (40.1)	105 (49.3)	0.06	67 (40.6)	75 (48.1)	0.18
Chronic obstructive pulmonary disease	30 (14.6)	37 (17.5)	0.43	22 (13.4)	26 (16.8)	0.44
Congestive heart failure	22 (10.7)	24 (11.3)	0.88	18 (11.0)	16 (10.3)	0.86
Cancer	28 (13.6)	32 (15.1)	0.68	23 (14.0)	24 (15.5)	0.75
Renal disease	21 (10.1)	25 (11.7)	0.64	15 (9.1)	18 (11.5)	0.58
Charlson comorbidity index (Mean (SD))[b]	1.5 (1.4)	1.7 (1.6)	0.22	1.4 (1.4)	1.7 (1.7)	0.13
Hospitalized prior year[a]	112 (54.6)	123 (58.0)	0.49	91 (55.5)	90 (57.7)	0.74
Nursing home prior year[a]	28 (13.7)	27 (12.7)	0.89	24 (14.6)	18 (11.5)	0.51
Enrollment hospitalization[a]						
ICU stay	41 (19.9)	31 (14.6)	0.16	28 (17.1)	25 (16.1)	0.88
Surgery	70 (34.0)	77 (36.3)	0.68	54 (32.9)	54 (34.8)	0.72
MRSA infection	92 (44.7)	82 (38.7)	0.23	75 (45.7)	66 (42.6)	0.58
Wound at discharge	109 (52.9)	110 (51.9)	0.85	87 (53.1)	83 (53.6)	0.93
Medical device at discharge	62 (30.1)	52 (24.5)	0.23	48 (29.3)	43 (27.7)	0.80
Bathing frequency[a]			0.02			0.05
More than once a day	29 (14.2)	20 (9.5)		27 (16.5)	17 (10.9)	
Every day	104 (50.7)	132 (62.6)		86 (52.4)	98 (62.8)	
Every other day	58 (28.3)	36 (17.1)		39 (23.8)	22 (14.1)	
Twice a week	11 (5.4)	16 (7.6)		10 (6.1)	12 (7.7)	
Once a week	3 (1.5)	5 (2.4)		2 (1.2)	5 (3.2)	
	0 (0)	2 (1.0)		0 (0)	2 (1.3)	
Bathing assistance needed[a]	33 (16.3)	32 (15.7)	0.89	24 (14.7)	25 (16.6)	0.76

Abbreviations: CLEAR (Changing Lives by Eradicating Antibiotic Resistance), MLST (multilocus sequence typing), SCC*mec* (staphylococcal cassette chromosome *mec*), *spa* (staphylococcal protein A gene), ICU (intensive care unit), MRSA (methicillin-resistant *Staphylococcus aureus*).
[a]Data reflect a response to a survey question or chart review. Not all participants responded to every question, and not all enrollment charts were received from recruiting hospitals despite a signed release request. Across the 2,121 trial participants, data were missing for 21 participants.
[b]Scores on the Charlson Comorbidity Index range from 0 to 10, with higher scores indicating more coexisting illness.

We evaluated 2 USA300 subgroups: a 2-criteria subgroup defined by presence of SCC*mec* type IV and MLST 8, and a 3-criteria subgroup additionally requiring *spa* type t008, the dominant *spa* type associated with USA300.[8] We allowed flexibility in *spa* type because previous work in Southern California, the location of the CLEAR Trial, identified several *spa* types closely related to t008 in the region, including t024.[8]

We assessed USA300 subgroups for the primary trial outcome, time to first MRSA infection by Centers for Disease Control and Prevention criteria as determined by blinded chart review, using unadjusted Cox proportional hazard models. We performed adjusted proportional hazard models accounting for participant demographics, comorbidities, presence of wounds or devices, history of hospitalization or nursing home residence in the year prior to enrollment, and receipt of anti-MRSA antibiotics as a time-varying covariate. We performed "per-protocol" and "as-treated" analyses to account for adherence to the decolonization protocol.

Results

Complete follow-up was achieved for 1,191 (56.2%) of 2,121 trial participants. Among 783 participants with MRSA strains tested, 420 (53.6%) met the 2-criteria USA300 definition and 321 (41.0%) met the 3-criteria definition with *spa* type t008. Among 99 participants in the 2-criteria cohort without t008, 38 *spa* types were identified; 76 participants carried *spa* types highly related to t008,[4] including t622 (N=47) and t024 (N=15), and 23 carried *spa* types that were not highly related to known healthcare-associated *spa* clonal complexes. Presence of ACME-arcA, PVL lukF, and

https://doi.org/10.1017/ice.2021.482 Published online by Cambridge University Press

Table 2. MRSA Infection Outcomes (First Infection per Person) per 365 Days of Follow-Up, According to CDC Criteria

	USA300 2-Criteria Definition MLST 8, SCC*mec* type IV		USA300 3-Criteria Definition MLST 8, SCC*mec* type IV, *spa* t008		Full Trial Population[6]		Trial Population Excluding USA 300 Carriers by Either Definition	
	Education N = 207	Decolonization N = 213	Education N = 165	Decolonization N = 156	Education N = 1063	Decolonization N = 1058	Education N = 856	Decolonization N = 845
	N (Events per Participant-Yr)	N (Events per Participant-Yr)	N (Events per Participant-Yr)	N (Events per Participant-Yr)	N (Events per Participant-Yr)	N (Events per Participant-Yr)	N (Events per Participant-Yr)	N (Events per Participant-Yr)
Total MRSA Infections	27 (0.149)	19 (0.099)	20 (0.137)	17 (0.123)	98 (0.139)	67 (0.098)	71 (0.136)	48 (0.098)
Skin or Soft-Tissue	15 (0.079)	10 (0.051)	11 (0.072)	10 (0.070)	34 (0.048)	32 (0.047)	19 (0.035)	22 (0.044)
Pneumonia	2 (0.010)	2 (0.010)	1 (0.006)	2 (0.013)	18 (0.026)	9 (0.013)	16 (0.029)	7 (0.014)
Primary Bloodstream/ Vascular	2 (0.010)	2 (0.010)	2 (0.013)	1 (0.007)	11 (0.016)	10 (0.015)	9 (0.016)	8 (0.016)
Bone or Joint	1 (0.005)	2 (0.010)	1 (0.006)	1 (0.007)	13 (0.019)	9 (0.013)	12 (0.022)	7 (0.014)
Surgical Site Infection	4 (0.020)	1 (0.005)	4 (0.026)	1 (0.007)	13 (0.019)	2 (0.003)	9 (0.016)	1 (0.002)
Urinary Tract Infection	1 (0.005)	0 (0)	0 (0)	0 (0)	3 (0.004)	2 (0.003)	2 (0.004)	2 (0.004)
Abdominal Infection	0 (0)	1 (0.005)	0 (0)	1 (0.007)	1 (0.001)	2 (0.003)	1 (0.002)	1 (0.002)
Other	2 (0.010)	1 (0.005)	1 (0.006)	1 (0.007)	5 (0.007)	1 (0.002)	3 (0.005)	0 (0.000)
Infection Involving Bacteremia	5 (0.028)	5 (0.026)	4 (0.027)	3 (0.022)	28 (0.040)	19 (0.028)	23 (0.044)	14 (0.029)

Abbreviations: CDC (Centers for Disease Control and Prevention), MLST (multilocus sequence typing), SCC*mec* (staphylococcal cassette chromosome *mec*), *spa* (staphylococcal protein A gene), MRSA (methicillin-resistant *Staphylococcus aureus*).

PVL lukS genes was detected in the majority of participants meeting 2-criteria (66.4%) and 3-criteria (86.7%) USA300 definitions.

Characteristics of USA300 carriers were similar to the full trial population (Table 1).[6] We note that the 2-criteria USA300 cohort had a greater proportion of male participants than the 3-criteria cohort. Frequency and rates of MRSA outcomes (first infection per person) are described in Table 2. For the overall trial population, the decolonization arm experienced a 0.041 absolute reduction (30% relative reduction) in MRSA infections per participant-year. In comparison, the 2-criteria USA300 cohort experienced a 0.050 absolute reduction (33% relative reduction) in MRSA infections per participant-year and the 3-criteria USA300 cohort experienced a 0.014 absolute reduction (10% relative reduction) in MRSA infections per participant-year. Compared to the overall trial population, USA300 carriers by either definition experienced higher proportions of skin and soft tissue infections, and lower proportions of bacteremia and bone and joint infections. Outcomes were similar when USA300 carriers by either definition were compared to those in the full trial cohort without USA300.

Supplementary Table 1 provides estimates of "per-protocol" and "as-treated" decolonization effects according to Cox proportional-hazard models. "Per-protocol" point estimates of hazard ratios (HR) were similar between USA300 carriers by the 2-criteria definition (0.59 (0.32, 1.09)) and the full trial population (0.61 (0.44, 0.85)), but were higher for the 3-criteria cohort with *spa* type 008 (0.82 (0.42, 1.59)). "As-treated" HR point estimates decreased with increased adherence for USA300 subgroups, consistent with overall trial findings.

Discussion

The CLEAR Trial demonstrated that post-discharge decolonization significantly reduced MRSA infections and hospitalizations. We found that USA300 carriers assigned to decolonization experienced a 33% reduction in MRSA infections compared to USA300 carriers assigned to education when using a 2-criteria definition. This was similar to the overall trial findings. However, when using a 3-criteria definition for USA300, only a 10% reduction was seen with decolonization. Explanations may include the fact that compared to the 2-criteria cohort, the 3-criteria cohort had an approximately 30% greater proportion of ACME/PVL genes, which may confer greater virulence, and a gender disparity of 30%, which may be associated with differential quality when applying decolonization. In a prior evaluation, we found that chlorhexidine concentration on the skin was nearly two-fold greater among female participants, and that female participants were more likely to use a mesh-sponge when applying chlorhexidine in the shower.[9]

This study has important limitations. First, ideal criteria for defining USA300 are still lacking.[10] To account for this, we evaluated 2 cohorts using different definitions for USA300. Second, while this study is limited to a 1-year follow-up period, it is known that MRSA infection risk is highest within 6 months of hospital discharge and normalizes after a year.[5] Finally, although the trial was not powered to evaluate a USA300 subgroup, it provides a valuable design for assessing the magnitude of strain-specific responsiveness to decolonization during a time when national rates of MRSA invasive disease have plateaued and USA300 is

https://doi.org/10.1017/ice.2021.482 Published online by Cambridge University Press

responsible for an increasing proportion of infections.[3] Larger studies may still be needed to examine differences in the outcomes and prevention of MRSA infections due to USA300 versus other strain-types.

Acknowledgements. We thank the trial participants and their families; the trial staff; and the staff of the many hospitals and nursing homes that supported the recruitment of participants in the trial.

Funding. This study was funded by the Centers for Disease Control and Prevention (Contract 75D30118C02890; PI: SS Huang) and supported in part by the Doris Duke Charitable Foundation (Grant # 2016092; PI: YH Grad).

Conflicts of Interest. The following investigators report conducting clinical studies in which participating hospitals and nursing homes received contributed antiseptic products from Stryker (GG, LH, JAM, LGM, RDS, SSH), Mölnlycke (LH, SSH), Xttrium Laboratories (GG, LH, JAM, LGM, RDS, SSH), and Medline (GG, LH, JAM, LGM, RDS, SSH). JAM reports receiving grant support and consulting fees from Achaogen and Medicines Company; grant support, consulting fees, and lecture fees from Allergan; grant support from Medline, consulting fees from Cempra, Melinta Therapeutics, Menarini Group, and Thermo Fisher Scientific; and research investigator funds from Science 37 and Lightship; and serving as cofounder of Expert Stewardship. LGM 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 advisory board fees from Tetraphase. YHG reports receiving grant support and consulting fees from Merck and advisory board fees from Day Zero Diagnostics. No other potential conflict of interest relevant to this article was reported.

Disclosure. These data were accepted as a SHEA Top Poster Abstract Award for the Sixth Decennial International Conference on Healthcare-Associated Infections, March 2020: Global Solutions to Antibiotic Resistance in Healthcare. The abstract was published in a supplementary issue of ICHE: Volume 41, Issue S1, DOI: https://doi.org/10.1017/ice.2020.565.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.482

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