Genomic Clusters of Methicillin-Resistant Staphylococcus aureus (MRSA) Causing Bloodstream Infections (BSIs) in Hospitalized Adults, 2018-19

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Background

- MRSA bloodstream infections (BSI) have 15-50% mortality
- Commonly diagnosed in U.S. hospitals
- Recent whole genome sequencing (WGS) study showed MRSA transmission from patients to healthcare workers (HCWs) & the environment in a hospital[1]
- WGS has shown that clonal cluster (CC) 8 & CC5 predominate among U.S. MRSA BSIs[2]
- WGS studies have demonstrated short- and long-term MRSA hospital outbreaks[3]
- It is unknown how often occult spread of MRSA occurs among patients to cause BSI

Methods

- Illumina HiSeq shotgun WGS of 106 sequential MRSA isolates from different adults with a BSI
- 2 Philadelphia, Pennsylvania academic hospitals in a single network (A & B)
- Cultures obtained July 2018-June 2019
- Genomic data analyzed with Staphopia Analysis Pipeline[4]
- Closely related (i.e., clustered) strains defined as <35 single nucleotide polymorphism (SNP) differences in core genome
- Clinical & demographic data extracted from electronic medical record (EMR)
  - In each subject cluster, recorded all hospital admissions 1 yr before first BSI & 1 yr after last BSI
  - Identified overlap of or sequential hospital/unit stays for clustered subjects at 3 hospitals (A, B, & C) in the university network

Results

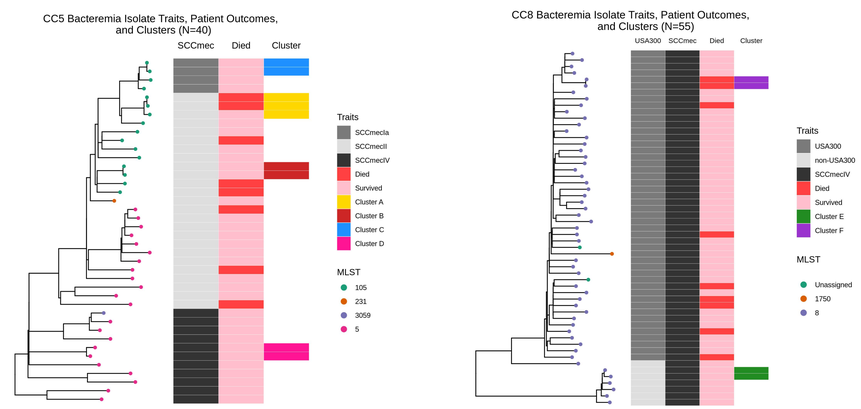
- Demographic & clinical subject characteristics shown in **Table 1**
  - In-hospital mortality was 17%
- **MRSA Genotypes**
  - 1 isolate had WGS data inadequate for analysis
  - 105 isolates with evaluable WGS data:
    - 40 CC5: 22 ST5 & 16 ST105 & 2 others (**Figure 1**)
    - 55 CC8: 48 USA300 & 7 others (**Figure 2**)
    - 9 MRSA isolates belonged to 3 other CCs
    - 1 isolate was *S. argenteus*
- **6 genomic clusters with 13 subjects (Figure 5)**
  - 4 were CC5 & 2 were CC8 (shown in **Figures 1-2**)
  - 11/13 index BSIs were cultured <48h after admission (i.e., CA-MRSA)
  - 4/13 (31%) subjects in clusters died during index BSI hospitalization
  - Cluster A (CC5) had 3 subjects & the other 5 clusters each had 2 subjects
  - Mean interval 108 d from first to last BSI diagnosis in a cluster
  - 3 clustered pairs had overlapping stays at Hospital A before the index BSI stay (n=1), during the index BSI stay (n=1), or both (n=1)
  - 4 clusters included pairs without temporally overlapping same-hospital stays
    - 2 of these 4 pairs had hospitalizations overlapping in time with 1 subject at Hospital A & the other at Hospital B prior to their index BSI stays
- **SNP distances**
  - No clear-cut clustering among the isolate genomes into transmission and non-transmission groups
  - Some isolate pairs separated by 40-80 SNPs (**Figures 3-4**)

Table 1: Subject demographic and clinical characteristics (n=106)

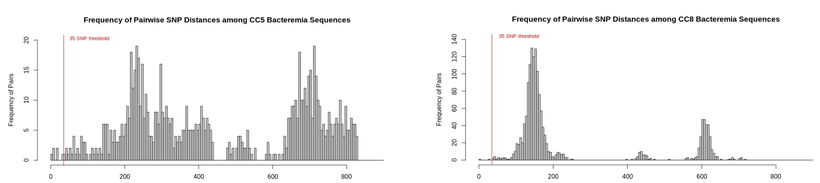
Demographics of Subjects	n=106 (%)
Age	
20-29 years	12 (11)
30-39 years	13 (12)
40-49 years	16 (15)
50-59 years	18 (17)
60-69 years	32 (30)
70+ years	15 (14)
Sex	
Male	55 (52)
Female	51 (48)
Race	
White	50 (47)
Black	49 (46)
Asian	1 (1)
Other / Unknown	6 (6)
Ethnicity	
Hispanic/Latino	2 (2)
Non-Hispanic/Latno	99 (93)
Unknown	5 (5)

Characteristic or Outcome of BSI	n=106 (%)
Source of BSI	
Central Venous Catheter	15 (14)
Skin or Soft Tissue Infection	19 (18)
Surgical Site Infection	4 (4)
Other / Uncertain Source	68 (65)
Hospital Where MRSA BSI Diagnosed	
A	65 (61)
B	41 (39)
Time of Diagnosis after Admission	
<48 hours[a]	83 (78)
>48 hours	23 (22)
Pitt Bacteremia Score (median, [IQR])	1 (0-3)
Endocarditis	
Yes – Native valve	23 (22)
Yes – Prosthetic valve	4 (4)
None	79 (75)
Metastatic Foci of Infection	
Septic Pulmonary Embolli	13 (12)
Other Metastatic Complication	40 (38)
In-hospital death	18 (17)

a. Includes 2 subjects with index blood cultures obtained prior to admission in an emergency department or clinic



Figures 1-2. Phylogeny of CC5 & CC8 isolates, indicating SCC*mec* type, USA300 genotype (among CC8 isolates), in-hospital mortality, & isolates in 6 Clusters (A-F); clusters A-F designations same as in Figure 5



Figures 3-4. Frequency of SNP differences among all CC5 (left) & CC8 (right) isolates; 6 clusters (Clusters A-D in CC5 & Clusters E & F in CC8) were defined by a 35-SNP difference cut-off (indicated by red lines)

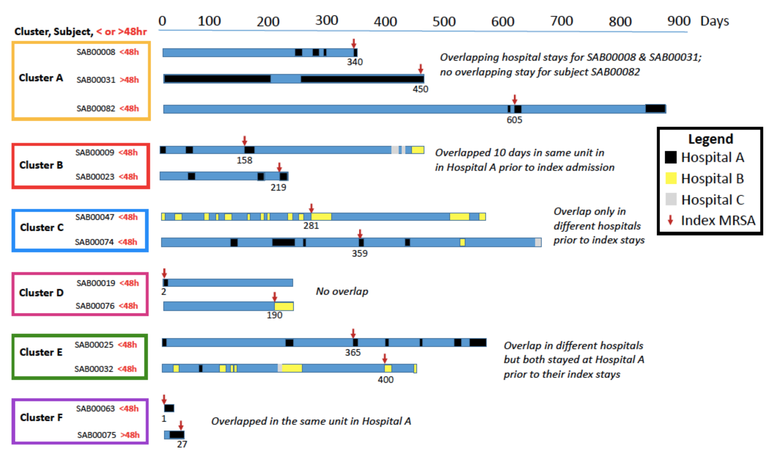


Figure 5: Admissions to Hospitals A, B, or C of 13 subjects (each in one row) in 6 MRSA clusters; **<48h:** index BSI culture obtained <48h after admission, **>48h**: index BSI culture obtained >48h after admission. Day 0: first admission for any cluster subject within 1 year prior to first cluster BSI.

Cluster A: n=3 (2 <48h & 1 >48h); 2 subjects had overlapping index & prior stays at Hospital A; the other subject (SAB00082;<48h) had no overlapping stay; all stayed at Hospital A before their own index admission.
Cluster B: n=2 subjects (both <48h) had prior 10-d overlapping stay (days 84-96) in same Hospital A unit.
Cluster C: n=2 subjects (both <48h) had prior overlapping admissions only to different hospitals (A & B).
Cluster D: n=2 subjects (both <48h) had no known prior overlapping hospitalizations.
Cluster E: n=2 subjects (both <48h) had previous, non-overlapping admissions to Hospital A & also simultaneous admissions to Hospitals A & B (days 231-234), respectively.
Cluster F: n=2 subjects (1 <48h & 1 >48h) had overlapping index stays in the same unit at Hospital A.

Conclusions

- WGS showed that 12% of MRSA BSI in 2 hospitals were caused by strains likely transmitted between subjects
- MRSA may have been transmitted by HCWs between 3 subject pairs with overlapping index or prior hospital admissions
- In other cases a persistent reservoir of MRSA likely existed in a hospital, or even across hospitals, resulting in transmission from one subject to another over an interval of many months
  - We also cannot rule out transmission in the community prior to admission
- Universal hospital WGS may detect MRSA hospital BSI outbreaks but requires examination of isolates collected over a long period of time in a hospital network

References

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