O450
1-hour Oral Session
New insights into host-pathogen interactions

Role of within-host evolution in Staphylococcus aureus infection

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Background: *Staphylococcus aureus* is a common nasal commensal that also causes invasive infection. Nasal *S. aureus* populations demonstrate significant within host diversity in asymptomatic carriage and during transmission. Less is known about the population dynamics in the setting of infection, though a case study showed dramatic narrowing of diversity in the transition from asymptomatic *S. aureus* carriage to bacteraemia. We report results of a systematic study of within-host evolution in invasive *S. aureus* disease.

Material/methods: 105 individuals with *S. aureus* cultured from both nasal swab and clinical samples were identified from the clinical laboratory of two UK hospitals. Clinical samples were blood culture (n=55) and pus, soft tissue and bone or joint samples (n=50). 5 or more individual colonies from each culture underwent whole genome sequencing on the Illumina HiSeq platform, yielding 1143 sequences. Variants were detected using both by mapping to reference strains and *de novo* assembly. Variants were typed for position on the reference genome, predicted effect on protein transcription and the population they occurred in. dN/dS was calculated using an approximate method, by comparing the expected ratio of non-synonymous to synonymous substitutions with that observed.

Results: 79 of 105 carriage populations demonstrated genomic diversity within the patient, compared to 39 disease populations. Up to 74 variants occurred within carriage populations, and up to 29 in disease. Mean pairwise distance within carriage had a median of 0.8 (IQR 0.4-3.5) while disease populations showed significantly lower mean pairwise distance with a median 0 (IQR 0-0.4) (Wilcoxon signed-rank test p= 1.03e-08).

10 individuals showed unrelated lineages in carriage and disease populations. 95 showed carriage and disease populations that were highly similar, but distinct: an identical genome was only sequenced from both sites in 21/95 cases. The mean pairwise distance between related populations had median of 2 (IQR 0.9-6.3): up to 66 variants separated related carriage and disease populations.

Of 1324 variants observed (see table), 8.7% caused premature stop codons, 3.2 times the rate reported in asymptomatic carriage. dN/dS was highest within carriage and lowest between carriage and disease populations, and both rates were higher than that reported in asymptomatic carriage, suggesting relative relaxation of selective pressure or adaptive change.

Conclusions: Carriage populations sampled in the setting of disease reveal diversity similar to that reported in asymptomatic carriage. Significant within host diversity arises between carriage and disease populations. Narrowed population diversity in disease, extensive diversity between carriage and disease populations and varying dN/dS provide evidence for selective pressures and within host adaptation during invasive *S.aureus* disease.

Variants	Non-coding	Synonymous	Non-synonymous	Premature stop codon	Total	dN/dS
Within carriage	144	91	319	61	615	0.73
Within disease	42	29	84	16	171	0.64
Distinguish carriage from disease	142	93	264	39	538	0.59