**Background and Methods**

**Background:**
*Staphylococcus epidermidis* is a leading cause of healthcare associated bacteremia, but the clinical course of *S. epidermidis* isolated from blood cultures ranges from contamination to serious deep seated infections. We tested the hypothesis that the genetic characteristics of *S. epidermidis* isolated from blood cultures are significantly associated with disease severity using whole genome sequencing (WGS).

**Methods:**
We performed WGS of 163 *S. epidermidis* isolates from a large prospective multicenter, randomized control trial that assessed the safety and efficacy of algorithm-based treatment of patients with staphylococcal bacteremia (ClinicalTrials.gov #NCT01191840). Patient’s infection types were divided into simple (including possible contamination), uncomplicated and complicated bacteremia. WGS was performed using Illumina Miseq, followed by in silico multi-locus sequence type identification and phylogenomic analysis using kSNP. Antimicrobial resistance determinants were identified using a custom database courtesy of UT-Southwestern (Jiwoong Kim, David Greenberg). A "rare" ST was defined as a ST with two or less isolates in the total cohort.

**Results**

*Figure 1. Phylogenomics of 163 *S. epidermidis* blood culture isolates compared to sequence type (ST) data. Agreement was present in 156/163 strains (96%).*

*Figure 2. Relationship between WGS based phylogenomics, ST, and clinical classification of *S. epidermidis* blood culture positive isolated.*

*Figure 3. Relationship between WGS phylogeny (left), ST (middle) and antimicrobial resistance (AMR) elements (heat-map). Red = present, green = absent. ST2/5 strains have more AMRs vs other STs (P < 0.01).*

*Figure 4. Analysis of clinical classification in relation to ST. ST2/5 strains were more likely to cause complicated infections and less likely to be classified as simple. The converse was true of “rare” STs.*

**Multivariate analysis:**
- ST2/5 strains were significantly associated with complicated infections
- $P = 0.01$
- Odds ratio = 4.01 with 95% confidence interval of 1.36-11.86

**Conclusions**

- First prospective, genomic analysis of blood culture positive *S. epidermidis* isolates with clinical correlates
- *S. epidermidis* blood culture isolates largely consist of large numbers of highly clonal strains by WGS analysis
- Significant clinical disease due to *S. epidermidis* strains is likely to be caused by multi-drug resistant, ST2 or ST5 clones
- Cases of complicated *S. epidermidis* infection were only observed for a limited number of STs (ST2, ST5, ST7, ST16, and ST32).