BAC DOOR: A Clinician Ranking Exercise for More Informative *Staphylococcus aureus* Bloodstream Infection Trial Design

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Background

- New therapies are needed for *S. aureus* bloodstream infection (SA-BSI).
- However, when comparing new antibiotic regimens, the standard noninferiority design fails to address the fundamental question of which treatment is better for patients.
- Desirability of Outcome Ranking (DOOR)[1] and partial credit[2] are novel methods for analysis of clinical trials. Patients are categorized according to overall outcomes, taking into account both benefits and harms.
- We conducted a study to develop a novel overall outcome to utilize DOOR or partial credit in future SA-BSI treatment trials.

Methods

- Twenty SA-BSI patient profiles were constructed to represent the range of experiences and outcomes observed in prior trials (Figure 1).
- Profiles described the efficacy, adverse events (AEs), symptomatology, and treatment adjustments of each patient during a theoretical trial comparing two treatments.
- Profiles were sent via a computerized survey to 43 ID clinicians working in the USA (28% pediatric). Respondents were asked to rank the 20 profiles from best to worst on the basis of desirability of overall outcome; profiles were presented in random order.
- We measured the consensus between respondent ranks. An overall outcome strategy based on the respondent consensus was developed using classification and regression tree (CART) analyses and team input.
- Consensus between ranks was measured with Spearman correlation and 95% confidence intervals

Results

- Forty-two (97%) respondents completed the survey. The distribution of the pairwise correlations between respondent rankings demonstrated moderately strong consensus (median correlation =0.69, IQR of 0.60-0.77).
- Respondents tended to differentiate best and worst profiles. However, a larger spread in responses was apparent for profiles in the middle (Figure 2).
- Features best discriminating rank were survival, severe AE, cure, infectious complications, and ongoing symptoms.
- Based on the CART analyses, the team developed an overall outcome strategy (Figure 3), which correlated strongly with the surveyed respondent ranking; r=0.89, 95% CI (0.73, 0.95).

Conclusions

- We created an ordinal outcome strategy incorporating benefits and harms as part of a global patient outcome in SA-BSI
- When comparing SA-BSI outcomes, clinicians place value not only on cure, but also on AEs, infectious complications, and symptom resolution.
- This ordinal outcome can be used for future trials comparing treatment strategies for SA-BSI, with the goal of improved differentiation between management approaches.
- This exercise demonstrates the process for translating benefits and risks into a syndrome-specific DOOR algorithm; this process can be repeated for other clinical syndromes
- Validation studies are being planned, incorporating patient preferences, analyzing data from recently completed trials, and upcoming SA-BSI treatment trials

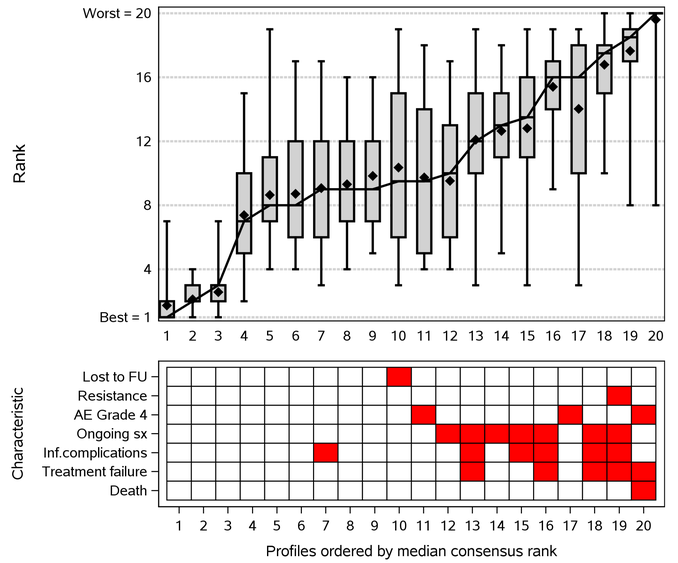
Figure 1. Sample Patient Profiles

57 y/o F has line-associated MRSA-BSI with a superficial thrombophlebitis during an admission for travel-associated pulmonary embolism treated with heparin then bridged to coumadin. Blood cultures are positive at day 3, negative thereafter. She is started on IV anti-staphylococcal antibiotics. She meets criteria for complicated SA-BSI and on day 14, she is randomized to oral therapy with drug A to complete 4 more weeks of therapy. Five days after discharge, she is readmitted for an UGI bleed and placed back on IV anti-staphylococcal antibiotics, which she receives for 5 days. She is discharged on PO therapy with drug A to complete a total 6-week course of therapy. At test-of-cure visit she has no signs of infection.

58 y/o M with diabetes and admitted with fever and left knee swelling. Initial blood cultures grow MRSA in 2/2 bottles, and he is taken to the OR the next day for I&D. He is started on IV anti-staphylococcal agents, and TTE is negative for endocarditis. He meets criteria for complicated SA-BSI and on day 13, he is randomized to oral therapy with drug A. Three days later he complains of new back pain and an MRI of his spine demonstrates an L1-2 diskitis/osteomyelitis with paravertebral phlegmon. A PICC is placed and he is switched back to IV therapy. He is evaluated by Neurosurgery, and no operative management is planned. He is discharged on day 28 to complete 2 more weeks of out-patient IV therapy. At the test-of-cure visit he is wheelchair bound because of continued pain, although this has improved since discharge and has no signs of recurrent infection.

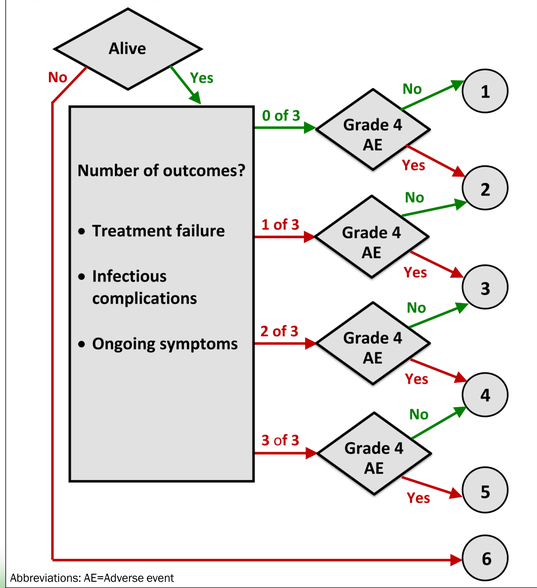
24 y/o F with history of IVDU presents with fever and R thigh swelling at prior injection site. Blood cultures grow MRSA, so she is started on an anti-staphylococcal IV antibiotic. Imaging of the leg demonstrates a pseudoaneurysm, and she is taken to the OR for repair and grafting. Poor quality TTE does not show vegetations. She refuses TEE. She clears her blood cultures on day 4 and has a PICC placed for ongoing antibiotics. She meets criteria for complicated SA-BSI. She is randomized on day 14 to oral drug A and discharged that day with a plan to complete 6 weeks of therapy. She returns to the emergency department on day 20 with severe nausea and vomiting, which is controlled by IV fluids and anti-emetics. She is discharged the same day with oral anti-emetics and instructed to complete her oral antibiotic course. She is lost to follow-up.

Figure 2. Distribution of Surveyed Respondent Rankings with Patient Profile Summaries



Abbreviations: AE=Adverse event; FU=Follow-up

Figure 3. DOOR Algorithm Based on Clinician Rankings.



Abbreviations: AE=Adverse event

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