European Federation of Pharmaceutical Industries and Associations

Development of Drugs for Bacteremia

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Bacteremia Guidance Issues

- EMA guidance suggests that bacteremia is not a primary diagnosis but represents ‘isolation from the blood of an organism....contributing to signs and symptoms of infection in a patient”
  - EFPIA agrees with this concept of associated bacteremia
- **Focus for today:** *S. aureus* bacteremia (SAB) is a unique and very important medical entity
  - Heterogeneity of infection makes study design challenging
  - Evidence base weak for clinical guidance
- Consider translating SAB features to bacteremia from MDR Gram-negative organisms

The Problem with *S. aureus* Bacteremia

- "The best way to manage SAB will remain unknown until the key clinical questions have been addressed by large, rigorous RCTs"
  - UK Infection Study Group, Thwaites et al Lancet 2011
- Regulatory pathway to encourage SAB trials?
- SAB can help inform considerations for other multi-drug resistant organisms

Key Themes for this review

- *S. aureus* bacteremia is a cluster of diverse syndromes
  - Mortality is actually highest when there is no obvious site
- Events defining outcomes are diverse
  - There is no obvious single best measure
  - Without a composite endpoint, clinical trials don't seem feasible

SAB: Wide Spectrum without Predominant Clinical Phenotype

- Uncomplicated bacteremia (no spread)
- Complicated bacteremia (persistence or spread)
- Bacteremia associated with removable focus
- Uncomplicated right-sided endocarditis in IV drug users with normal valves and no 2^{ndry} sites
- Complicated right-sided endocarditis (all others)
- Left-sided endocarditis

- Bacteremia without identified source common and associated with high mortality

High Mortality in SAB: particularly in patients w/o a site identified

- 549 UK patients – MSSA and MRSA
- Removable: IV catheter: 21% (113/549)
- Removable, other source: 20% (110/549)
- Site not established 19% (101/549)
- Not removable : 40% (213/549)
  - Soft tissue comprised 34%
  - Endocarditis 5%
- 24% mortality: 32% within 3 days; 40%: 4-14 days

- Highest mortality in “not established” group (45%)
  - SAB Prospective Study Thwaites. PLoS ONE: Dec 2010

The Evidence Base: Daptomycin all comers trial *

- ~2.5 yrs to enroll comparative trial vs. standards of care (vancomycin, oxacillin etc)
  - Spectrum of bacteremia including catheter-related BSI
  - 30 daptomycin pts with right-sided endocarditis
- 246 pts randomized- 158 completed
- 44.2% daptomycin success vs. 41.7 comparator
  - Difference = 2.4% ; 95% CI: -10.2 to 15.1%
- Bacteremia subsets numerically similar outcomes between daptomycin and comparator
  - Similar results in RIE to SOC
- Indication granted for RIE and skin source subsets but not general bacteremia

***EMEA EPAR Scientific Discussion**

All-Comers SAB Trial: ways to optimise precision and analysis

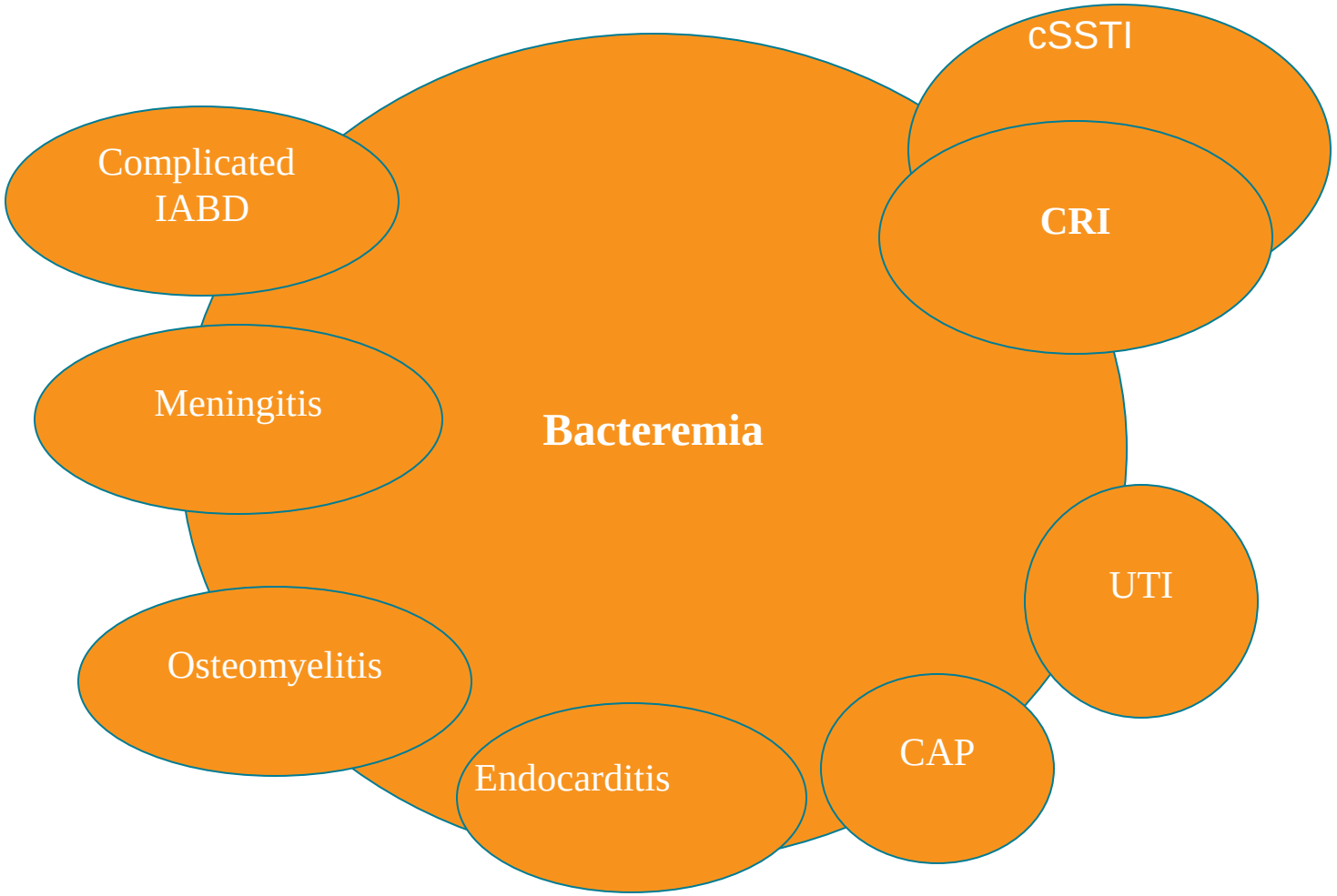
- Adjust predictive baseline pre-specified variables
  - Length of bacteremia
  - Endocarditis location (R, L)
  - Removable focus
  - Time in Hospital prior to bacteremia
  - Age
  - Time of prior antibiotics
- Composite Primary Endpoint
  - Time to clearance of bacteremia
  - Overall Investigator assessment of Clinical response (normalization of signs and symptoms of infection at EOT and proof of cure)
  - Time to clearance of select SIRS measures (BP, tachycardia)

Advantages and Disadvantages of Composite Endpoints

- Statistical efficiency and reduced sample size requirements.
  - Increased events rates
- Avoiding adjustments for multiple comparisons
- Avoiding arbitrary choice of a single outcome when many may be of equal importance.
- Allows the measurement of “overall” benefit of the treatment
- Useful when a single primary endpoint is hard to choose

- Difficulty in assigning weights to components
  - Improvement can be driven by less important component(s) of the composite endpoint
- Effects observed on individual components may not move in the same direction.
- Need to adjust for multiplicity to draw conclusions about the individual components

Relationship of Bacteremia and Traditional Indications



Knirsch: FDA Anti-infective Advisory Committee Meeting. October 14, 2004:

MDR gram negative product studied across traditional indications; Ways to optimise precision and analysis

- Adjust predictive baseline pre-specified variables
  - Source of bacteremia
  - Removable focus
  - Time in Hospital prior to bacteremia
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Bacteremia labeling – important information for a treating physician

- *S. aureus* bacteremia could be studied as a single entity as part of a spectrum of disease
  - Model-based statistics to adjust for baseline factors and length of therapy and pre-specify composite primary endpoint
  - Include *S. aureus* catheter-related bacteremia
- MDR Pathogens: accumulate sufficient clinical data to support an indication for bacteremia
- Two options:
  - With robust non-clinical data and PD data in several tissue sites, multiple organisms in bacteremia should be possible
  - Additionally, single pathogen from numerous different sites could be aggregated for bacteremia labeling considerations

Summary

- *S. aureus* bacteremia is
  - Medically relevant information for prescribers
  - Amenable to a special pathway studying full spectrum of entity as a secondary indication including Catheter BSIs
  - Appropriate as a place to use statistical techniques to enhance efficiency of study
- "Associated bacteremia" labeling medically relevant for MDR Gram-negative bacteremia
  - Organism-specific bacteremia labeling from across indications from a Tier C program
  - Multiple MDR organisms from a single indication when strong *in vitro* microbiology, PK/PD, and animal data from a Tier B program