



European Federation of Pharmaceutical
Industries and Associations

Development of Drugs for Bacteremia

Mark Kunkel MD

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 that concept of associated bacteremia makes sense
- However, *S. aureus* bacteremia is a unique and very important medical entity
 - Heterogeneity of infection makes design challenging
 - Need to find regulatory path for study
- Catheter-related BSI is another very important syndrome that needs a regulatory path

Bacteremia labeling: Options

- EFPIA agrees that secondary bacteremia associated with a specific infection could be included as part of the label for that indication
 - Organism-specific indication lacking source qualification would be difficult without extensive data in many indications
 - However, it is not clear that this is more informative than “associated bacteremia” labeling for several key indications
- *S. aureus* bacteremia could possibly be studied as part of a spectrum
- Catheter-related bacteremia (CRBSI) would be a separate entity

Spectrum of *S. aureus* bacteremia

S. aureus comprises a spectrum

- Uncomplicated bacteremia (no spread)
 - Generally secondary to known source
- Complicated bacteremia (persistence or spread)
- Uncomplicated right-sided endocarditis in IV drug users with normal valves and no 2ndry sites
- Complicated right-sided endocarditis (all others)
- Left-sided endocarditis

CRBSI is unique and separate entity

Approach to *S. aureus* bacteremia

Routes to study are needed for this important syndrome

- It is comprised of multiple subgroups representing the spectrum of *S. aureus* bacteremia
- No one subgroup is large enough: Need to study in toto
 - Patient population needs patients from all subgroups
 - Enrollment is technically possible but still difficult
 - Daptomycin 235 patients (over >3 years with enormous effort)
- Endpoint analysis for group as whole
 - Then analyses by subsets
- May require standardization of diagnosis and adjunctive therapies (TEE, surgery, rifampin, etc.)

Catheter-related Bloodstream Infections

- Current draft guidance provides no path
- Rationale for excluding: Heterogeneous disease
- Could consider CRBSI as part of a spectrum of catheter-related infection
 - Sub-type of cSSSI (signs at site, positive tip or cath blood culture)
 - Positive peripheral blood culture concordant with above could be defined as CRBSI
- *S. aureus* (and possibly GNR) as part of this diagnosis
 - Path for Coagulase-negative *Staphylococcus* more difficult
 - Concordant catheter and peripheral blood could meet definition

Catheter-related Infection

Possible Path

- Consider studying as a type of cSSSI
- First analyze the whole patient group
 - Then subgroups of skin and local infection and true CRBSI
 - Need to differentiate coag-neg *Staphylococcus* from *S. aureus*/GNR
- Linezolid CRI study used this approach
 - 339 pts in category of cSSSI (CRI) with 169 meeting definition of CRBSI
 - Made the study technically feasible but still 3 ½ years to enroll
- Careful exclusion of “complicated infection”
 - E.g., endocarditis or endovascular, other focus
- Requires careful design, site selection, monitoring
- Provides valuable medical information about common & important entity

Summary

- “Associated bacteremia” labeling makes sense
- *S. aureus* bacteremia is
 - Very important medically
 - Might be amenable to a special pathway
- Catheter-related bloodstream infection
 - Might be amendable to study as a subset of complicated skin infections