Primary Bacteremia due to *Staphylococcus aureus* (PBSA) and Catheter-Related Blood Stream Infections (CRBSI).

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I. Introduction

The FDA's approach to prescription drug labeling for claims related to bacteremia has varied over time based on changes in the science and advice from the Anti-Infective Drugs Advisory Committee (AIDAC). The Agency established the precedent of granting indications in drug labeling based on a particular disease syndrome or site of infection, given the known differences between the natural history and pathophysiology of infectious diseases at various body sites. Experience has validated this approach in that FDA has reviewed drugs that were effective in one body site yet were not proven effective in infections at other body sites. Approvals based on bacteremia alone may not account for potential differences in drug efficacy based on the primary site of infection. Therefore, FDA has taken the position to include data on outcomes in bacteremic patients within the context of a primary site of infection.

In 1999, AIDAC members suggested that catheter-related blood stream infections (CRBSI) should be a potential source of study, and FDA issued draft guidance on drug development for this indication. At the time, the committee members outlined the potential pitfalls in performing scientifically rigorous studies in this area. Drug sponsors engaged in studying CRBSI have encountered many of these issues. In addition, other drug sponsors have approached FDA with studies seeking to evaluate the efficacy and safety of drugs in primary bacteremia due to *Staphylococcus aureus* (PBSA). Many *S aureus* bacteremias without an obvious source may have a portal of entry related to an intravascular catheter. In this advisory meeting, we will discuss the scientific, regulatory and practical issues of a potential indication in primary bacteremia due to *S. aureus* as well as revisit the guidance on catheter related bloodstream infections.

This briefing document outlines the regulatory history of indications related to bacteremia, as well as CRBSI. It includes a discussion of issues that have been encountered in attempting to study CRBSI and how such data might be reflected in product labeling. Additionally, we summarize the epidemiology and natural history of *S. aureus* bacteremia, and relate this to scientific issues in clinical trial design to support such a claim.

The Agency seeks the Committee's advice on resolution of the problems encountered by sponsors in following the current guidance on CRBSI; the merits of a PBSA indication; and the optimal approach to the design, conduct and analysis of CRBSI and PBSA clinical trials.

II. Regulatory History

Prior to 1992, the labeling of anti-infective drugs included the terms *bacteremia* and *septicemia*. Bacteremia was defined as an infection accompanied by one positive blood culture, whereas septicemia was defined by two positive blood cultures. Analyses of clinical data used in granting those indications involved pooling data from patients with infections associated with *concurrent* bacteremia, often from diverse unrelated infections (e.g., UTI, pneumonia). In addition, the clinical context was variable, as transient bacteremia, bacteremia secondary to a known source, and bacteremia of unknown origin were considered together, despite their differing pathophysiology.

In 1992, the FDA published the "Guidance to Industry on Clinical Development and Labeling of Anti-Infective Drug Products" (also called the "Points to Consider" document) to assist sponsors in formulating development plans for anti-infective drug products[1]. The Points to Consider document contained information related to the Agency's perspective on specific indications, recognizing the differences in pathophysiology between diverse diseases. The term "indication" referred to "the treatment of infections at a specific body site(s) due to a specified susceptible microorganism(s)"[2]. At that time, FDA raised questions about the appropriateness of "bacteremia" indications as they related to infections at specific body sites.

These questions resulted in a meeting of the AIDAC in 1993. Committee members discussed the issues related to "bacteremic sepsis" as a potential new anti-infective drug product indication.[3] At the time, "bacteremic sepsis" represented new terminology that was proposed to add specificity and clarity to the previously used terms "bacteremia" and "septicemia".

The then-proposed new indication incorporated definitions of sepsis and bacteremia, as provided in a consensus document of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) published in 1992.[4] The ACCP/SCCM Consensus document defined a hierarchy of syndromes from infection to severe sepsis. The document defined *infection* as "a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms". The document defined *bacteremia* as the laboratory recovery of viable bacteria in the blood. The systemic inflammatory response to severe clinical insults was termed *systemic inflammatory response syndrome* (SIRS), manifested by two or more of the listed criteria: temperature >38 ºC or <36 ºC, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or PaCO2 <32 torr, and WBC count of >12,000 cells/mm^3, <4000 cells/mm^3, or >10% bands (immature forms). SIRS could be of infectious or non-infectious etiologies. *Sepsis* was defined as patients with signs and symptoms of SIRS due to an infectious etiology. The document defined *severe sepsis* as sepsis associated with hypotension, hypoperfusion, and organ dysfunction. Drug sponsors defined the potential new indication of "bacteremic sepsis" as SIRS due to infection with associated positive blood cultures, but without the hypotension, hypoperfusion, and organ dysfunction that characterize severe sepsis.

While these definitions are useful in clinical practice, Committee members at the 1993 AIDAC identified several issues related to clinical trial design and prescription drug product labeling that served as focal points for discussion. These issues included 1) whether bacteremic sepsis was a clinically meaningful disease entity; 2) the heterogeneity of the patient population under study; 3) the clinical significance of a positive blood culture, in terms of adding specificity to the identification of the underlying infecting microorganism; and 4) whether drug efficacy in treating an organism in the blood can be extrapolated to efficacy in infections at particular body sites, the putative source of the bacteremia.

In their comments about the use of the terms "bacteremia" and "septicemia" in product labeling, the AIDAC expressed concerns about the overall lack of specificity of the definitions, the heterogeneity of the patient population, the pooling of data involving bacteremias with varied sites of origin and differing underlying pathophysiology, and the inability to distinguish patients with SIRS who had concurrent bacteremia from those without bacteremia on a clinical basis.

Following extensive discussion, the 1993 AIDAC members recommended elimination of "bacteremic sepsis" as an indication, continuing to use the site of infection in defining an indication for an anti-infective drug, and including bacteremia in product labeling in the context of site-specific infection (e.g., "community-acquired pneumonia with concurrent bacteremia").

During the five years following the 1993 AIDAC meeting until the AIDAC meeting in 1998, there were no anti-infective drugs approved for the indication of bacteremia. However, the issue of bacteremia as an indication was again considered by the 1998 AIDAC.[5] The discussion arose in light of the rising incidence of bacteremia due to antimicrobial resistant (predominantly Gram-positive) microorganisms, the increased incidence of bacteremias without an identifiable source, and the use of data involving patients with positive blood cultures to enhance the specificity of diagnosis in clinical trials.

Following extensive discussion, the 1998 AIDAC members concluded that product labeling regarding "bacteremia", secondary to an identified site of infection, should *not* be considered as a separate indication. Rather, the Committee advised the Agency that it should be retained within the context of the site-specific indications. In addition, the 1998 AIDAC identified primary bacteremia (including catheter-related bloodstream infections) as a potential area for study. Catheter-related bloodstream infections (CRBSI) were considered a potential focus for future investigation. Committee members considered this indication a potential source of useful information, due to the increased incidence of CRBSI in hospitals, growing antimicrobial drug resistance among bacteria with limited treatment options for such infections, and the lack of controlled clinical trials for antimicrobial drugs for the treatment and prevention of CRBSI.

Following the 1998 Advisory meeting, the FDA formed a CRBSI Working Group to develop a Guidance Document for Industry on Drug Development for CRBSI (see

Appendix A). The preliminary guidance was presented at an AIDAC meeting in 1999. [6]
Committee members identified several issues related to drug development for the
treatment of CRBSI:

(1) The patient population in CRBSI studies could be very heterogeneous with
varying host factors and underlying illnesses, different types of intravascular
catheters, and diverse causative microorganisms that differ in virulence and
natural history of disease. Varying host factors could include different clinical
presentations of illness in adults compared to pediatric patients, differing
approaches to patients with prosthetic devices, and differences in individual
patient requirements for long-term intravenous access.

(2) Difficulties might be encountered in establishing the catheter as the source of
bacteremia. The issue reflects potential problems in acquiring culture data from
catheters, which may then necessitate screening a large number of patients to
enroll sufficient cases with a diagnosis of bacteremia related to a catheter. The
large sample size might require substantial time for patient accrual.

(3) The committee discussed issues related to the microbiological criteria for
establishing proof of CRBSI. Certain microbiological tests used to diagnose
CRBSI, such as quantitative blood cultures, might not be available in some
institutions. The committee concluded that additional data were necessary on
other methods of diagnosis, such as the differential time to positive blood culture
and various types of catheter cultures. Obtaining these data is complicated by the
lack of a gold standard against which to compare these tests.

(4) The lack of a known (or proven) magnitude of the benefit of antimicrobial
treatment for certain etiologic microorganisms, such as *Staphylococcus
epidermidis*, which are often the most common organisms in CRBSIs.

(5) The lack of standardized procedures for the management of an intravascular
catheter in CRBSI. Such differences in management may affect outcomes
independent of the effect of the antimicrobial administered. There was discussion
about whether factors such as the type of catheter (tunneled vs non-tunneled) and
suspected pathogen (such as *S. epidermidis* vs. *S. aureus*) should be considered in
decisions related to catheter removal.

(6) Issues related to establishing the specificity of the diagnosis of CRBSI due to
some common skin pathogens. The committee discussed appropriate laboratory
testing to establish the concordance of catheter and blood culture isolates, such as
pulse-field gel electrophoresis for *S. epidermidis.*

Many of these scientific and practical issues remain, and sponsors have a dilemma in
trying to complete their studies of CRBSI.

III. Drug Sponsors Experiences with CRBSI Trials

Since the introduction in 1999 of the CRBSI guidance, several sponsors have attempted
studies in this indication. The Agency has received feedback from some of those sponsors
on problems they have encountered in the study of CRBSI. In April 2004, FDA co-
sponsored a public workshop on antimicrobial drug development in which some data on

experiences with CRBSI trials were presented. Dr. Timothy Henkel (Vicuron Pharmaceuticals) outlined the practical and scientific issues in CRBSI trials from his company's perspective. In Dr. Henkel's experience, investigators were identifying the majority of potential patients for study by screening for positive blood cultures, rather than identifying patients by clinical inclusion criteria. Using blood cultures as the screening method, 75 of 2639 (2.8%) patients screened were subsequently enrolled in the study over a period of 17 months. Just as the AIDAC Committee discussed previously, the most difficult piece of data to obtain was culture data from catheters. Thirty percent (30%) of screened patients could not be enrolled due to inadequate culture data, with the microbiologic evidence from catheter cultures the most common missing piece of information. Another twenty percent (20%) were excluded on the basis of prior antibiotic usage. Additional challenges noted by Dr. Henkel included other points previously discussed: heterogeneity of the patient population, issues with inclusion/exclusion criteria, microbiologic methods not the standard of care at many institutions, and lack of an approved comparator.

Other sponsors have met with the Agency to discuss their experience with similar clinical trials aimed at garnering a claim for CRBSI. Their experience confirms the difficulty in obtaining sufficient numbers of patients, along with confirmatory microbiology, in CRBSI trials. Sponsors have indicated that, despite enrollment of patients based on clinical criteria consistent with catheter-related infection, along with removal and culturing of the catheter, only about a quarter of patients enrolled meet the most liberal of the microbiologic definitions for CRBSI (concordant growth of an organism from peripheral blood and catheter site exudate).

Since the AIDAC in October 1999, the Infectious Diseases Society of America, the American College of Critical Care Medicine, and the Society for Healthcare Epidemiology of America have published guidelines for the diagnosis and management of CRBSI. [7] These guidelines represent a compilation of the available evidence from the literature and the strength of that evidence to assist clinicians in clinical practice. However, while the clinician is provided with an algorithmic approach to diagnosis, catheter management, and antimicrobial treatment strategy based on the type of catheter and pathogen responsible, none of these recommendations is based on evidence from randomized, controlled clinical trials. The recommendations serve the practitioner at the bedside, but do not necessarily provide sufficient information on the optimal design and analytic plan for a formal clinical trial in CRBSI.

The issue of lack of a gold standard for diagnosis of CRBSI, discussed thoroughly at the AIDAC meeting in 1999, still remains. Since 1999, authors have published several studies on alternative methods of diagnosis of CRBSI. It is difficult to compare sensitivity and specificity of these methods in the absence of a benchmark. Different studies apply different, sometimes widely variant, definitions for CRBSI. In addition, some of the methods (such as quantitative peripheral and catheter blood cultures, differential incubation time and thus positive culture result for catheter and peripheral blood cultures, catheter tip cultures processed by the roll-plate, Brun-Buisson, or sonication methods) may vary in sensitivity and specificity of diagnosis, depending on

the patient population or catheter type studied. There have been additional studies in the published literature on the utility of differential time to positive culture result for catheter versus peripheral blood cultures. The studies demonstrating the utility of this method in diagnosis have been performed primarily in immunocompromised patients with the majority of patients having tunneled catheters.[8,9,10,11] The results of differential time to positive-culture studies have not been validated in a medical-surgical ICU population with short-term catheters.[12] Additionally, the assessment of sensitivity and specificity of this method has been made on the basis of quantitative blood cultures and semi-quantitative or quantitative catheter tip cultures, with no single method serving as a validated standard.

At the April 2004 FDA Workshop, academic investigators and drug sponsors suggested the possibility and discussed the merits of studying the indication of treatment of primary bacteremia due to *Staphylococcus aureus* (PBSA). In this context, FDA would like to review the existing CRBSI guidance document and how it may relate to a potential indication of PBSA. Given the difficulties experienced by sponsors in the design and conduct of CRBSI trials, the Agency seeks guidance from AIDAC members on how to move forward to address the CRBSI indication, as well as the merits of a claim for treating primary bacteremia due to *S. aureus*.

In this document, we have included discussion points for both primary bacteremia due to *S. aureus* and catheter related bloodstream infections. At the Advisory meeting, you will be provided with an integrated set of questions so that both topics can be discussed at the same time.

Issues for Discussion – Catheter-Related Blood Stream Infections

1. Should FDA maintain the CRBSI Guidance Document in its present form?
2. Are there modifications to the CRBSI Guidance that Committee members would suggest that would allow more efficient enrollment of patients while still maintaining adequate specificity of diagnosis and gaining useful information for clinicians?
3. Can sponsors include data on patients who may have bacteremia due to *S. aureus,* secondary to a presumed portal of entry of an intravascular catheter, as part of a PBSA indication? Could patients with CRBSI and patients with PBSA be handled within a unified guidance document?
4. Can sponsors garner an indication of "catheter site infections", with or without bacteremia, as part of another indication (i.e., complicated skin and skin structure infections)? How would one ensure the specificity of diagnosis in patients with minimal signs and symptoms of skin infection and where the organism cultured from blood and/or skin is normal skin flora?

IV. Potential Indication of Primary *S. aureus* Bacteremia

At the April 2004 FDA co-sponsored public workshop, investigators and sponsors addressed the topic of a potential indication for PBSA. The participants discussed the potential advantages of this indication relative to an indication for CRBSI. A PBSA indication would concentrate on only one organism, which causes serious disease and for which there may be data on the magnitude of the treatment effect of antimicrobials. In general, the magnitude of the treatment effect for some organisms, like *S. epidermidis*, *Corynebacteria* and some *Bacillus* species, is not known. In addition, it may be more difficult to differentiate true infection from false-positive blood cultures for these common skin organisms. A primary bacteremia claim would also eliminate the most common difficulty in CRBSI trials, namely the link of the disease to a catheter as the source. As discussed below, many cases of PBSA may be linked to a portal of entry from an intravascular device, but this is often a diagnosis of exclusion, and diagnosis in clinical practice is often "presumed". In addition, as discussed previously, there is no validated gold standard for diagnosing CRBSI. Finally, there may be the potential to acquire data on the efficacy of antimicrobials in patients with infective endocarditis (IE) from such trials.

However, many of the challenges present in trials of CRBSI, such as a heterogeneous patient population, may still be present in clinical trials of PBSA. We will discuss these issues in light of the epidemiology and natural history of bacteremia due to *S. aureus*.

Epidemiology and Natural History of *Staphylococcus aureus* Bacteremia (SAB)

Epidemiology
From 1980-1989, the rates of SAB from all sites of infection reported to the National Nosocomial Infection Surveillance (NNIS) system increased in teaching hospitals.[13] *Staphylococcus aureus* has become the second most common bloodstream isolate, contributing to 16% of all hospital-acquired bacteremias.[14] The rate of both community and hospital acquired bacteremia due to *S.aureus* has increased over the last few years.[15] Rates of IE due to *S.aureus* have also increased.[16,17,18] The majority of IE are still community-acquired, however there is an increasing incidence of hospital-acquired IE due to *S.aureus*.[19]

*"Primary" **S. aureus** Bacteremia without a known source*

The source of *S. aureus* bacteremia is an important consideration when attempting to design clinical trials to examine the efficacy of an antimicrobial. Recent examples have shown that an antimicrobial may be effective in disease caused by a given pathogen at one body site and yet not be proven effective in disease caused by that same pathogen at a different body site. It is hypothesized and certainly logical that all patients with PBSA must have some occult portal of entry of the organism into the blood stream. However, in clinical trials of PBSA, it will be important to rule out a known primary source of

infection in a standard way in the protocol. Patients with a known primary source of infection, such as skin infections and pneumonia, can be studied in clinical trials of that particular body site.

Data show that most patients with bacteremia due to *S. aureus* have a known site of infection. This may limit the available patient population for clinical trials of PBSA. In one study of 37 patients with *S.aureus* bacteremia, a primary source was identified in 24 patients (62%). [20] Mylotte et al. reported that a primary focus was identified in 91/114 (80%) episodes of SAB. [21] In a study of 79 non-drug addict patients, a primary focus was identified in 59 (75%) patients. [22]

The following graph shows the distribution of primary foci in patients with SAB from a compilation of studies over five decades. Presently, about 20% of patients with SAB have no identified primary focus of infection.[23]

(■) Intravenous catheter; (◆) unknown; (●) postoperative wound; (▲) skin.
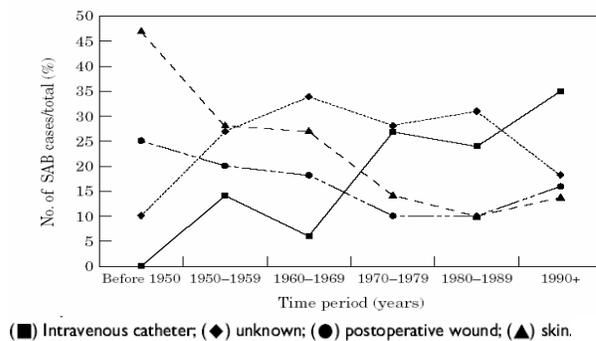
S. aureus *Bacteremia and Catheters*

Much of the disease attributed to "primary" SAB is related to intravascular devices. Intravascular device-associated SAB accounts for a large fraction of the documented increase in hospital-acquired SAB. In a study by Steinberg et al., an increase in the number of intravascular device-associated bacteremias accounted for 70% of the increase in the number of nosocomial *S.aureus* bloodstream infections. [15] Jensen et al. found an intravenous catheter as the source in 45% of patients with hospital-acquired SAB. [23] In a study by Fowler et al. of 103 patients with SAB, 69 (67%) had an intravascular catheter as the source. [24] An intravascular catheter was considered the source if 1) there was evidence of inflammation at the catheter insertion site, or 2) a catheter-tip culture was positive for *S.aureus*, or both, and 3) there was no evidence of an alternative source. Community-acquired disease is increasingly associated with the use of intravascular devices.[19,25] This may be a reflection of changes in medical care with increasing number of patients receiving medical care in outpatient settings.[32] In a study from the Netherlands, 25/75 (33%) patients had a central venous catheter in place at the time of diagnosis, and in 12 of these, the catheter was used in a community setting. [26]

Heterogeneity of Patient Populations with S. aureus *Bacteremia*

There appear to be differences in host factors and clinical presentations within the group of patients with PBSA. This has important clinical implications, as different clinical presentations may result in different lengths of therapy. Patient heterogeneity also has important implications for the designs and analysis of clinical trials, as different patient populations may have different success rates even with appropriate therapy. Clinical trials attempt to measure drug effects independent of the natural history of the disease, host factors and other confounding factors. Failure to account for important differences in patient populations may result in measured differences between therapies in a clinical trial that may not be related to drug effects but to other confounding factors. While randomization gives an equal *probability* of distribution of these factors between arms of the trial, randomization is not foolproof. One study that evaluated the importance of randomization and blinding showed that at least one prognostic factor was not distributed equally between arms of the trial in 14.0% of trials that were blinded and randomized. [27] Unequal distribution of factors between the arms of a trial may have an impact on the interpretation of the results. The importance of unequal distribution of various factors not only depends on the statistical significance of the difference in the distribution of the factor between the study arms but on the strength of the association of the outcome with that factor. In other words, one should consider small differences in the distribution of factors between study arms as clinically significant if the factor has a known large impact on outcomes, even though the differences are not statistically significant. [28] Small differences between arms of a PBSA trial in the presence of important factors like infective endocarditis have the potential to affect the interpretation of the results, even if the differences between study arms are not statistically different. Therefore, one should attempt to account for these important factors prior to enrollment in a clinical trial. We outline some of the potentially important factors in PBSA trials below.

Community versus nosocomial acquisition

The proportions of the location of acquisition of SAB vary between studies partly due to differences in the definitions of community versus hospital acquired disease (positive culture within 48 hours or 72 hours of hospitalization). Additionally, some authors differentiate community-acquired disease into those with any health care contact in the preceding few months, while in other reports these patients are not clearly separated.

Investigators studied the prevalence of community-acquired SAB in a one-year period in Connecticut. A total of 48% of SAB were community-acquired and the incidence was 17/100,000. Sixty-two percent (120/192) of patients with community-acquired SAB had contact with the healthcare system in the preceding 12 months. [29] This is similar to results of the study by Jensen et al. where 131/278 (47%) SAB were community acquired. [23] Mylotte et al. reported slightly higher rates (58%) using 72 hours as the cut off to differentiate community acquired from hospital acquired disease. [30]

The difference between community-acquired and hospital-acquired disease may be important in clinical trials, as patients with community-acquired SAB have a higher

likelihood of developing metastatic disease and IE. There appear to be differences in clinical success rates between patients with and without metastatic disease and those with and without IE. The higher rate of metastatic disease may be related to the prolonged duration of bacteremia prior to detection. [31] In their series of 278 patients, Jensen et al. found that intravenous catheters and post operative wound infections were most often the primary foci of SAB infection in hospital-acquired cases, while skin lesions were more common in community-acquired cases. Patients with community-acquired disease were more likely to have an unknown portal of entry, a higher frequency of secondary infection, and a slightly higher mortality. [23]

Complicated versus uncomplicated bacteremia due to *S. aureus*

There appear to be differences in clinical success rates between patients with what has been termed "complicated" compared to "uncomplicated" bacteremia due to *S. aureus*. Again, this may be an important factor to account for in clinical trials. Investigators prospectively evaluated risk factors for developing complicated SAB in 724 adults hospitalized with SAB from 1994-1999. They defined complicated SAB as attributable mortality, complicated infection, embolic stroke, or recurrent *S.aureus* infection during the 12-week follow up period. Patients with complicated infection had a site of infection remote from the primary focus caused by hematogenous seeding or extension of infection beyond the primary focus. Of the 722 patients with follow up data, 310 had complicated SAB and 412 had uncomplicated SAB. Risk factors for complicated SAB were positive blood culture at 48-96 hours, community acquisition, skin examination with findings suggesting acute systemic infection (defined as presence of petechiae, vasculitis, infarcts, ecchymoses, or pustules), and persistent fever at 72 hours. [32]

While the criteria described above for distinguishing complicated from uncomplicated infection may be useful in clinical practice, their application may be more problematic in the setting of a clinical trial. Some of the criteria, such as presence of persistent fever, and persistently positive blood cultures, are not measurable at the time of enrollment in the trial. In addition, some of these factors may differ between an effective and an ineffective drug. Using such criteria would confuse the natural history of the disease with the ability of the drug to affect the course of the illness.

SAB with and without endocarditis

Given the differences in clinical success rates between patients with and without IE, it will be important to make an accurate diagnosis of the presence or absence of IE in PBSA trials. The information necessary to make an accurate diagnosis of IE, such as echocardiographic data, often will not be available at the time of randomization. Clinical differentiation of SAB from endocarditis can be difficult in the absence of typical clinical features of IE, such as a new murmur, embolic lesions etc. Nolan and Beaty suggested three useful bedside criteria for predicting presence of IE in patients with SAB; community-acquisition, no apparent primary focus, and metastatic foci.

IE may be difficult to diagnose on clinical grounds alone and echocardiography may be necessary to make the diagnosis. In a study by Røder et al. from Denmark, IE was not diagnosed clinically in over half of the 152 pathologically confirmed cases due to *S.aureus*. In a prospective study by Fowler et al., 103 patients with SAB were evaluated by transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE). Clinical evidence of IE was seen in only 7 (7%) of patients. [24]

The numbers of patients with PBSA who have IE may be substantial. The prevalence of IE in patients with community-acquired SAB varies from 6-64%.[33] Among 104 patients with SAB, 33 (32%) had echocardiographically confirmed endocarditis; 23 were community acquired and 10 were nosocomially acquired. [34,19] Increasing numbers of cases of IE are now nosocomially acquired. [15] In a study by Fowler et al., the authors noted clinical differences between patients with community acquired versus hospital acquired IE. Patients with community acquired disease were more likely to have vascular phenomena and no evident source for bacteremia while those with hospital acquired IE were more likely to have IE due to MRSA. Out of 59 cases of IE due to *S.aureus* identified over a 3-year period, 27 (45.8%) patients had hospital-acquired infection. In over half of the patients an intravascular device was the presumed source of infection. [19]

The most common foci of *S. aureus* infection in patients with a known site of infection are usually from skin, soft tissue, or bone but IE can occur in patients who have no detectable primary focus.[22] In the study by Fowler et al. in the 26 cases with IE, 3 had no focus of infection, 7 had deep tissue infection, and 16 had a catheter focus. [24] In a study by Chang et al., of the 505 cases with SAB 64 (13%) had IE, seven of whom had new endocarditis as a complication of SAB. [35] Risk factors for development of IE identified were: native valve disease [OR 4.5, 2.0-9.9], presence of prosthetic valve [OR 10.5, 2.5-43.7], persistent bacteremia [OR 10.5, 3.3-16.6], IVDU [OR 3.2, 1.2-8.6], unidentifiable portal of entry [OR 3.3, 1.3-6.6], history of prior endocarditis [OR 10.0, 2.0-50.0], and community acquisition [OR 2.9, 1.4-4.9].

Metastatic Disease

Metastatic infection may complicate SAB. This is an important consideration given the implications for treatment and considerations as to whether metastatic foci developing on therapy are indicative of clinical failure. The efficacy of various drugs may differ at distant metastatic sites. For example, a drug which does not have penetration into the central nervous system (CNS) may not have efficacy in treating metastatic CNS disease. Metastatic complications may be evident at first presentation or may become evident weeks later. Ringberg et al. found metastatic complications in 53% of patients.[36] In a study of 39 patients with SAB, suppurative sequelae were reported in 9 (23%) patients, all of whom were diagnosed after the first week of bacteremia. [20] Jensen et al. found that secondary foci developed in approximately 30% of patients with community-acquired disease and only 5% of those with hospital-acquired disease. [23] In a retrospective study of 281 patients with SAB, common sites of metastatic disease were joints (36%), kidneys

(29%), CNS (28%), skin (16%), intervertebral disc (15%). More than one metastatic site of infection was present in half the cases. [37]

Prospective studies have examined risk factors for metastatic infection in patients with SAB. [21, 23, 38, 39] These risk factors may be important exclusions for clinical trials in PBSA. Underlying cardiac disease is an important risk factor for development of IE in patients with SAB. [40] Besides rheumatic heart disease, other structural anomalies like mitral valve prolapse, bicuspid aortic valve, senile/degenerative aortic valve stenosis or sclerosis, prosthetic valves, and previous IE are common predisposing conditions. [41] In a study of 44 patients with prosthetic cardiac valves who developed SAB, 15 (34%) developed IE. [42]

Presence of an implanted prosthetic device is a risk factor for the development of metastatic complications. Among 33 prospectively identified patients with a permanent pacemaker or implantable cardioverter defibrillator who developed SAB, the rate of confirmed device infection was 45.4%. [43] Non cardiac prosthetic devices such as orthopedic devices are also at risk of seeding during an episode of SAB. [44] The presence of an indwelling foreign body is also an important risk factor for subsequent relapse. [45]

Patients with community-acquired SAB have a higher likelihood of developing metastatic disease. In a prospective study of patients with SAB, the prevalence of endocarditis in patients with community-acquired SAB was 21% (43/206), 12% (11/95) in hemodialysis patients, and 5% (10/204) in patients with hospital-acquired SAB. [46]

A prospective study of 104 patients examined the role of persistent bacteremia in predicting secondary metastatic infections. Fifty-three patients had negative blood cultures between 24-48 hours after effective therapy and 51 had sustained bacteremia. Metastatic infections developed in 59% of patients with sustained bacteremia versus 17% in those without sustained bacteremia. [46] This data indicates that the occurrence of metastatic disease after some initial period on therapy may be an indicator of a less effective therapy.

Length of Therapy

Decisions regarding the length of therapy usually depend on the extent of disease and on host risk factors. Patients with complicated infections such as IE, deep tissue abscesses, and infected prosthetic devices usually receive a minimum of 4-6 weeks of intravenous therapy and surgical intervention as clinically indicated. [41] Appropriate length of therapy for patients with uncomplicated SAB, especially those associated with intravascular catheters is still unclear. Some investigators have proposed that a 14-day course of therapy will suffice. [47] Other investigators have proposed longer length of therapy based upon the finding of increased complication rates in patients treated with short-course therapy. [48] The Infectious Diseases Society of America (IDSA), the American College of Critical Care Medicine (for the Society of Critical Care Medicine), and the Society for Healthcare Epidemiology of America have issued recommendations for the management and diagnosis of catheter-related infections. [7]

For the purposes of clinical trials, it would be important to standardize the length of treatment for various clinical presentations. In this way, one can compare patients with similar clinical presentations across arms of the trial. If length of therapy is not standardized, more patients in one arm of the trial may receive longer duration of therapy than the other arm for the same clinical presentation. Any differences in outcome in this setting may be related to differences in length of therapy rather than inherent differences between the drugs.

Outcomes

About one third of patients with SAB develop one or more metastatic complications. [37, 38] Acute systemic complications such as septic shock, acute respiratory distress syndrome (ARDS), and disseminated intravascular coagulation (DIC) occur most commonly within 48 hours of an initial positive blood culture. Higher complication rates have been reported by others; 90% of 113 South African patients with community-acquired SAB and no history of injection drug use had one or more complications. [31]

In the study by Verhagen et al., 35% of patients with SAB developed complications. Twelve percent of patients had a relapse within 3 months of follow up. [26] Similar relapse rates have been reported by others. [23, 38] Eradication of the focus of infection is associated with lower recurrence rates. [23] Failure to remove an intravascular device was the most important risk factor for treatment failure in one study. [38] Some studies have reported that relapse rates are higher in patients with persistent bacteremia =3 days, failure to remove the source, and vancomycin therapy. [49] However, other studies with vancomycin show similar success rates to patients treated with anti-staphylococcal penicillins.

Reported mortality rates in studies have ranged from 16%-43%. [50] Studies have differed in the patient populations included, definitions of mortality and sample sizes. Mortality is highest in the first 30 days after onset of bacteremia; 83-90% of patients died within 28-30 after onset of bacteremia. [30, 51] Factors associated with increased mortality include acute severity of illness at onset of SAB, unknown source of infection, and older age. [30,31,52,53] The mortality rate for patients with eradicable foci is lower than if the focus is non-eradicable. [23] Kim et al. showed that mortality in patients with non-eradicated foci was higher than in those with eradicated foci [OR 4.17 (1.09-3.62)]. [51]

V. Issues in Describing an Indication and Designing/Analyzing Clinical Trials in PBSA

There are several issues prompting the Agency to seek the advice of Committee members in determining whether PBSA should be designated as a separate indication. The first of these is the importance of studying this indication in providing information to prescribing physicians and their patients. Based on comments at the April 2004 Workshop, academicians and drug sponsors indicated that data from clinical trials in PBSA may provide information on efficacy and safety of an antimicrobial in a more serious yet relatively common disease and address some of the challenges in studying CRBSI. Data

from PBSA trials may provide information on CRBSI due to *S. aureus* as well as provide information on treatment of IE.

Secondly, FDA will ask the committee to discuss what kinds of in vitro, animal model data, and prior clinical trials in other serious infections (e.g., pneumonia, complicated skin) would be recommended prior to, or in some circumstances concurrent with, trials in PBSA. Ideally, a more comprehensive clinical development program would include evidence from treatment of patients with serious Staph aureus infections in other indications (e.g., pneumonia, complicated skin, etc.) including some bacteremic patients.

Finally, FDA would like the Committee to discuss is the ideal, yet practical, clinical trial design for PBSA. How best would investigators exclude patients with a known primary focus of infection due to *S. aureus?* When would investigators perform evaluations of patients with echocardiography to determine which patients may have endocarditis? FDA will ask the Committee to discuss appropriate comparator regimens, as well as clinical and microbiologic endpoints.

In this document, we have included discussion points for both primary bacteremia due to *S. aureus* and catheter related bloodstream infections. At the Advisory meeting, you will be provided with an integrated set of questions so that both topics can be discussed at the same time.

Issues for discussion- PBSA

1. Would data from clinical trials in patients with primary bacteremia due to *S. aureus* provide useful information for clinicians? Should PBSA be designated as a separate indication?
2. Are there additional preclinical studies (e.g., animal models of endocarditis) that would be recommended prior to initiation of clinical trials in patients with PBSA?
3. What results from other clinical trials (e.g., pneumonia, complicated skin infections) would, in general, be expected prior to proceeding with clinical trials in PBSA?
4. How would one define PBSA in terms of both clinical findings at enrollment as well as positive blood cultures to ensure the specificity of the diagnosis? What kind of standard evaluation should patients receive prior to enrollment to rule out a known source of infection? What kind of evaluation should patients receive to rule out endocarditis?
5. How would one differentiate occult sites of infection in the bacteremic patient that may be present at time of enrollment from bacteremic patients who develop site specific lesions (e.g., heart valve, bone) while on therapy?

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