DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (AIDAC) MEETING

Discussion of Issues Related to Clinical Trial Design and Analysis in Studying Bacteremia Due to Staphylococcus aureus and Catheter Related Bacteremia

Thursday, October 14, 2004

8:20 a.m.

Hilton Gaithersburg
The Ballroom
620 Perry Parkway
Gaithersburg, Maryland

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James E. Leggett, Jr., M.D., Chair
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John H. Powers, M.D.
Alfred Sorbello, D.O.
Janice Soreth, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. LEGGETT: Good morning. Today we are gathered to discuss issues related to clinical-trial design and analysis in studying bacteremia due to Staphylococcus aureus as well as issues related to clinical-trial design or analysis in studying catheter-related bacteremia.

It is going to be, I hope, not a terribly eventful day but eventful, nonetheless. I think that the problem that we are faced with, as clinicians, I faced on Friday when I was asked to see two patients, one a recently end-stage renal-disease patient with diabetes who has had three MRSA hemodialysis catheter infections since July when she started dialysis requiring the removal of the catheter and, at the same time, was called to see a patient because they had Gram-positive cocci in clusters from their one of two blood cultures and it turned out to be coagulate-negative Staph and who cared.

So I think that is going to be sort of the

crux of a lot of the problems today.

To get started, why don't we go around the table and have everyone introduce themselves.

DR. MAXWELL: I'm Celia Maxwell, the Assistant Vice President for Health Sciences at Howard University, an adult infectious diseases specialist.

DR. BRADLEY: I am John Bradley, Pediatric Infectious Diseases, from Children's Hospital in San Diego.

DR. OHL: Chris Ohl, Section on Infectious Diseases, Wake Forest University School of Medicine.

DR. HILTON: Joan Hilton. I am on the Biostatistics Faculty at University of California, San Francisco.

DR. MURRAY: Pat Murray, Director of Microbiology at the NIH Clinical Center.

DR. RELLER: Barth Reller, Division of Infectious Diseases and International Health and Director of Clinical Microbiology, Duke University Medical Center.

DR. LEGGETT: Jim Leggett, Infectious Diseases, Providence Portland Medical Center and the Oregon Health and Sciences University.

DR. CROSS: Alan Cross, Center for Vaccine Development, University of Maryland.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. MALDONADO: Sam Maldonado, Global and Regulatory Affairs, Johnson & Johnson. I am the industry representative to this committee.

DR. PATTERSON: Jan Patterson, Medicine Infectious Diseases, University of Texas Health Science Center, San Antonio and South Texas Veterans Healthcare System.

DR. THEILMAN: Nathan Theilman, Division of Infectious Diseases and International Health, Duke University Medical Center.

DR. PORETZ: Donald Poretz, Infectious Diseases in Fairfax, Virginia.

DR. NAMBIAR: Sumathi Nambiar, Division of Anti-Infective Drug Products, FDA.

DR. SORBELLO: Fred Sorbello, Medical

Officer, FDA.

DR. POWERS: John Powers, Lead Medical Officer for Antimicrobial Drug Development and Resistance Initiatives in ODE IV at FDA.

DR. SORETH: Good morning. I am Janice Soreth, the Division Director for Anti-Infectives. Let me take the opportunity to introduce in absentia our Office Director, Dr. Mark Goldberger, who is on his way. But another person who is actually here and who directs a sister division, that of Special Pathogens and Immunologic Drugs which also regulates antibiotic development. That would be Dr. Renata Albrecht who sits behind me here.

MS. JAIN: I am Shalini Jain, Executive Secretary for the Anti-Infective Drugs Advisory Committee.

Conflict of Interest Statement

MS. JAIN: Before we begin the meeting, I need to read a conflict-of-interest statement. The following announcement addresses the issue of conflict of interest issues associated with this

meeting and is made a part of the record to preclude even the appearance of such.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors in academic institutions.

All Special Government Employees have been screened for their financial interests as they may apply to the general topics at hand. To determine if any conflict of interest existed, the agency has reviewed the agenda and all relevant financial interests as reported by the meeting participants.

The Food and Drug Administration has granted general-matters waivers to the Special Government Employees participating in this meeting who require a waiver until Title 18 United States Code Section 208. A copy of waiver statements may be obtained by submitted a written request to the agency's Freedom of Information Office, Room 12A-30

of the Parklawn Building.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they may apply to each member, consultant and guest speaker. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Samuel Maldonado is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Maldonado's role on this committee is to represent industry interests in general and not any one particular company. Dr. Maldonado is employed by Johnson & Johnson.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants has a financial interest, the participants' involvement and their

exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. LEGGETT: Janice, would you like to start?

Opening Comments

DR. SORETH: Good morning, Dr. Leggett and special thanks for the academic quarter this morning, members of the advisory committee, FDA and industry colleagues and other members of the audience.

(Slide.)

I would like to begin today's talks by telling you what we are going to talk about today followed by actually talking about it, then summarizing what we already told you as a segue to the discussion. I promise we will finish before midnight.

This is the story of blood and guidance going a bit bad, that of bacteremia as an indication.

(Slide.)

I am going to take us first through the District of Columbia, Rockville and White Oak--you will understand what I mean in just a moment--followed by a tour, very briefly, of Hollywood, the Washington Redskins, the NHL lockout, Monday morning quarterbacking--that would be the discussion period--and wrapping up with credits. I promise you I have not yet lost my mind.

(Slide.)

We are back in the District of Columbia. It is pre-1965. I am in second grade. We have been talking about bacteremia, sepsis, bacteremic sepsis, septicemia, primary bacteremia and secondary bacteremia for a long, long time, ever since the FDA was solely located in the District.

As far as the Org chart goes back then, and this is all oral history, we were the Bureau of

Biological and Physical Sciences, the Division of Pharmacology and we were a branch, I think, of Antibiotics. As I said, my knowledge of this era is entirely derivative.

(Slide.)

Let's fast-forward to Rockville of the '70s and the '80s where the language for bacteremia and septicemia began to make it into package inserts. We will hear more about this historical framework and its details through to the 1990s and the present from Dr. Fred Sorbello this morning.

The Org chart was changing. We were becoming the Bureau of Biological and Physical Sciences, Division of Pharmacology to the Bureau of Drugs and Biologics, Division of Anti-Infective and, finally, the Center for Drug Evaluation and Research. I realize only now I forgot to put Crystal City on there because, once we went from the District, we went to Crystal City which is in Virginia and then, ultimately, to Rockville and Gaithersburg, which is where we are now.

The Division was morphing at the same

time. It was growing. Back in the '70s and '80s, we were the Division of Anti-Infectives. We were one entity that took care of regulation of antibiotics, anti-infectives, anti-parasitics, topical antiseptics, dermatologics, ophthalmologics, anti-fungals, T.B. drugs and antivirals. I am sure I left something out. Let me know at the break.

There was a split, then, that happened in the latter '80s. I think it was about '88 when the development of HIV therapies took off, as it should. So we split and became the Division of Antiviral Drugs as well as the Division of Anti-Infectives. The Antiviral therapies together with the Antifungals and the TB drugs, then, went to the Division of Antivirals.

This is the late '80's, early '90's.

(Slide.)

By the time we hit mid-'90's, maybe about 1996, we, as two divisions, were large again. Portfolios were growing. So we decided to morph at that point into a third division. So the

Ur-Division, as I like to call it, of Anti-Infectives then became Anti-Infectives, Antivirals and Special Pathogens and Immunologic Drug Products directed by Dr. Renata Albrecht.

The portfolio from Anti-Infectives of quinolones split off to Special Pathogens. I believe chronic fatigue and AIDS wasting type of drugs and transplant products and antifungals and antiparasitics also went to Special Pathogens.

So we are now three divisions under the leadership of Dr. Mark Goldberger. It is pertinent--the background is pertinent to today because the topics really touch all of us within the office and particularly Anti-Infectives and Special Pathogens. We need to be careful as we write the music that we sing from the same sheet of music.

I think more on the history of what we have struggled with as a word, bacteremia, septicemia, will be discussed later today not only by Dr. Fred Sorbello but also, in terms of clinical-trial design considerations by Dr. John

Powers, by Dr. Janice Pohlman as well as Dr. Sumathi Nambiar.

(Slide.)

As to the future, we are moving in 2005, we are told, to White Oak. Shalini, correct me if I am wrong, but I think all that AC meetings will take place there.

MS. JAIN: Actually no. They won't be able to actually accommodate the size.

DR. SORETH: Wonderful. Okay. To be determined later. Shalini was just saying that we won't necessarily have the AC meetings at White Oak. It is our combined campus, a dream that we have maintained at FDA for a long, long time. Some would say a nightmare, but whatever. It is off New Hampshire around the Beltway for Washingtonians.

This is the laboratory building. Our building is off to that side. I am a little challenged directionally. I would submit to you that we sincerely hope to have the guidance in this arena tucked away by the time we move to White Oak.

So, see, we have a challenge.

(Slide.)

Hollywood, where we are told nothing is impossible, where every scientist should remove the word "impossible" from his lexicon. Christopher Reeve. Nothing is impossible.

(Slide.)

Except maybe when it comes to the breakdown of skin, invasion of the blood stream and infection of the patient followed by cardiac arrest, heart failure, coma and death, for Superman was no match for a bloodstream infection.

(Slide.)

I think our meeting today will highlight that it takes extraordinary individuals to recognize that investment and effort in the discovery of new antibiotics and in the treatments for serious infections, like Staphylococcus aureus bacteremia, are indeed worth it in the long run. And I know that some of these extraordinary individuals are in this room today.

They are prescribing physicians. They are

academicians. They are industry colleagues. They are FDA colleagues. They are support staff all of whom have, at heart, the same mission.

(Slide.)

So what do the Skins have to do with this? Well, you have to ask yourself the question what do Joe Gibbs, who is the Head Coach of the Washington Redskins, and the FDA have in common? I will preface my comments by saying I am a die-hard Eagles fan but it is not why I say this.

Just like Joe Gibbs, we thought we had put all the right pieces together on the team with the catheter-related blood-stream infection guidance. That is 1999 and Dr. Janice Pohlman will tell us a lot more about that later today. And, just like Joe Gibbs, we watched as the monster just wouldn't get up.

(Slide.)

We discussed the catheter-related blood-stream infection guidance hereafter known as CRBSI at a 1999 advisory committee meeting. Most of you were probably not here then because we had a

different committee there. But I know Dr. Barth Reller was there. The U.S. stats would tell us that roughly there are 200,000 or 400,000 episodes per year. We should be able to study it.

Mortality attributable somewhere between 10, 25 percent; we thought a definable case definition--we thought. Lo and behold, sponsors, many of them, now tell us there are numerous reasons why they have hit the boards. But I would ask, don't blame it on my heart; blame it on my youth.

(Slide.)

The NHL lockout is pertinent here because success, beyond being tied to this year's salary cap, is determined not by knowing where the puck is, rather knowing where the puck is going to be, which is sometimes, maybe often, unpredictable which is probably why they don't want a salary cap in the first place. But the increasing incidence of Staph aureus bacteremia paralleled by a rise in infective endocarditis, I think, foreshadows where major players need to position themselves to win,

to develop effective therapies whose risk/benefit ratio we think we understand so that, ultimately, patients and their prescribing physicians can benefit from this.

(Slide.)

The issues for discussion are many. Dr. John Powers will cover these in great detail. I have made some excerpts and highlights from his talk that will come later today. But I want you to bear them in mind as you go through today's discussions and talks. Should primary bacteremia due to Staph aureus, PBSA, be an indication? And what exactly would a healthy development program look like? What patient populations would be included in such a program?

And, just as importantly, would there be populations that should be excluded, because we are not really sure they have an infection? Do they have a lab finding? Should endocarditis due to Staph aureus be a separate indication?

(Slide.)

More issues for discussion. Should we

grant a separate catheter-related blood-stream infection indication in its own right? Does it have merit? Does it lack merit? Or, do we fold it into a more general clinical-trial experience and product label under the rubric of primary bacteremia due to Staph aureus or under the rubric of complicated skin infections?

If we go the separate way, what additional information would you suggest be collected before, or while, treating other serious Staph aureus infections?

(Slide.)

Finally, what role do preclinical and early clinical studies play in setting the stage for faster, larger clinical trials? We are cognizant of the fact that, in many ways, in drug development, as in life, time and money are our enemies. We sweat the small stuff and we ask you today to do the same.

How many positive blood cultures are required prior to entry into a primary bacteremia due to Staph aureus clinical trial?

(Slide.)

Last, screening patients for admission into these clinical trials appears to be complicated. Do you have any thoughts or advice for us as to a general approach?

(Slide.)

I would like to thank Shalini Jain, our Exec Sec contact and organizer for today's meeting who answered numerous phone calls, E-mails and cell-phone calls way later than anyone should have made them, myself included; our Office Director, Mark Goldberger; John Powers; Ed Cox: and Leo Chan; and, at the Division level, my ever supportive reliable deputy, Lilian Gravrilovich and members of the division, Sumathi Nambiar, Janice Pohlman and Fred Sorbello.

I will stop there and turn the podium back over to Dr. Leggett.

DR. LEGGETT: Thank you.

Let's move on to the Regulatory History of Bacteremia Indications which will be done by Dr. Sorbello.

Regulatory History of Bacteremia Indications

DR. SORBELLO: Good morning. I am Fred Sorbello, Medical Officer at the Division of Anti-Infective Drug Products at FDA.

(Slide.)

My presentation today will focus on the regulatory history of bacteremia and some of the early regulatory history of catheter-related blood-stream infections as labeled blood-stream infection indications.

(Slide.)

I wanted to start with an historical time line to help to focus a little bit on the history of the development of this whole issue from a regulatory perspective. It really began prior to 1992, 1993. As Dr. Soreth had described, there were various types of terminology that were being used in the setting of labeling for blood-stream infections.

In 1992, the FDA developed a document called Points to Consider. This was a very important document because it was designed to

assist investigators on how to formulate drug-development plans for infective agents. Since that time, there have been several anti-infective drug advisory committee meeting where the issue has been discussed, including 1993, 1998 and 1999 and, obviously, at the meeting today.

(Slide.)

Just to give you a little bit of a perspective on the terminology that has been used for blood-stream infections in antimicrobial, I just have a chart to kind of compare the historical terminology versus what is used currently. Historically, labels would include terms such as bacteremia or septicemia or bacteremia/septicemia, bacterial septicemia or septicemia (including bacteremia.)

Today, what is used currently is terminology that is in accordance with the Points to Consider document which is basically site-specific indications with bacteremia included if bacteremic patients were involved and assessed adequately within the particular trials.

To give you a little more perspective on the labeling indications prior to 1992, 1993, the terms "bacteremia" and "septicemia" were those that were used most commonly. These were defined as infections that were accompanied by certain types of laboratory criteria.

Bacteremia related to the evidence of one positive blood culture, septicemia with two positive blood cultures. It is important to note that, at that time, there were no specific clinical-trial protocols that were really relevant to those indications. The data was derived by pooling data on bacteremic patients from trials that involved different sites of infection; for example, trials that might have looked at pneumonia or urinary-tract infections where bacteremic patients may have been enrolled.

Also the clinical context was bit varied in that patients with either transient bacteremias or, as I mentioned, bacteremias where there may be an identifiable focus or even bacteremias of unknown origin could have been included amongst

this pooled data.

(Slide.)

1992, Points to Consider, a very critical document that was developed. Again, it did contain relevant information on the agency's perspective on specific indications for anti-infective drugs. It really was an attempt to recognize that different types of infections had different pathophysiology.

The way labeled indications were indicated was they were referred to as the treatment of an infection at a specific body site due to a specified susceptible microorganism. Drug-development guidelines were provided with the document so that accurate information could be complied on both the efficacy and safety of the drug and that information could later be described in product labeling.

(Slide.)

The 1993 Anti-Infective Drug Advisory Committee focused a bit on this issue of bacteremia in the setting of two issues. Number one, the consensus document developed by the American

College of Chest Physicians and the Society of Critical Care Medicine where definitions were published regarding terms such as sepsis and multi-organ failure. In addition, a pharmaceutical sponsor had proposed a new indication termed bacteremic sepsis in an attempt to try to both add some specificity and clarify some of the previous terminology in order to do a particular drug-development study. The definition of bacteremic sepsis included some of the material from the consensus document.

(Slide.)

Just to review briefly the consensus-document definitions, infection was described as a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion or normally sterile host tissue by those organisms.

Bacteremia was defined as a laboratory finding associated with the presence of viable bacteremia in the blood. The systemic inflammatory response was a response that can occur with a

multitude of clinical entities and it was basically manifested by two or more of the criteria that were listed which was temperature greater than 30 degrees C or less than 36 degrees C, an elevated heart rate of greater than 90 beats per minute, respiratory rate greater than 20 beats per minute or a PA-CO2 of less than 32, an elevated white count of 12,000 or a low white-blood count of less than 4,000 or 10 percent bands.

Sepsis, then, was defined as an infected patient who exhibited a systemic inflammatory response.

(Slide.)

This is a Venn diagram which is adapted from the paper in Critical Care Medicine which described the consensus document in the definitions. But it was an attempt to try to show how some of these concepts merge, again illustrating that there is a large focus of infected patients and some of those patients will exhibit a systemic inflammatory response syndrome. Those that do are considered septic.

Bacteremia essentially refers to the laboratory finding of bacteremia in a blood culture. Again, just keep in mind that there can be other non-infectious causes that can produce a systemic inflammatory response including burns, ischemia, pancreatitis and others.

(Slide.)

So, getting back to bacteremic sepsis with the consensus definitions and concepts in mind, bacteremic sepsis was defined at the time as SIRS, systemic inflammatory response syndrome, due to an infection that was associated with positive blood cultures but was without hypotension, hypoperfusion or any evidence of organ dysfunction.

The definition implied, but it didn't state, that the patient would have an identifiable focus of infection. Now, when this concept was discussed by the 1993 Anti-Infective Drug Advisory Committee, there were a number of issues that were reviewed. I am just going to mention some of them here at this point.

One is bacteremic sepsis really a

clinically meaningful entity. Could we, really, on a clinical basis, identify patients who had that entity. Number two, there were concerns that the population would be rather heterogeneous because you might be looking at patients with different types of underlying diseases, different states of immunosuppression, immunocompetence, for instance.

Positive blood cultures; it was certainly felt that they do add confirmation and specificity in identifying an infecting organism but there was some discussion about whether positive blood cultures could, in some way, be a marker of prognosis.

Another issue was the efficacy of a drug in treating a blood-stream infection and whether it would be possible to extrapolate the efficacy in clearing a blood-stream infection to being comparable effective in treating an infection that is, for example, deep within a certain body tissue or site that might be the source for that bacteremia.

(Slide.)

So, amongst the discussion at the time in 1993, it was felt that the terms bacteremia and septicemia as had been used lacked specificity of definition. Again, there were concerns about the patient populations that would be studied. There were concerns about the whole concept of pooling data from various sites of origin, effective origin for bacteremias and, lastly, whether or not it would be possible on a clinical basis to actually identify a person who had sepsis infection with a systemic inflammatory response who would have a positive blood culture versus those who would have clinical findings without a positive blood culture, was it really clinically meaningful and could it be identified on the clinical basis.

(Slide.)

The recommendations from the Anti-Infective Drug Advisory Committee at the time in '93 was, again, to focus labeling related to the site of infection, site-specific labeling as had been described through the Points to Consider Document and then including bacteremia within that

context if it was applicable rather than using terms such as bacteremia or bacteremic sepsis.

(Slide.)

Now over the following five years, there were no new drugs that had been approved with the indication of bacteremia. But bacteremia and this whole concept of blood-stream-infection indications resurfaced again back in 1998 at the Anti-Infective Drug Advisory Committee.

In particular, the main topic referred to catheter-related blood-stream infections. The issues that brought the issue up for discussion included the observed rising incidence of bacteremia due to resistant Gram-positive bacteria in particular, the increased incidence that was noted of intravenous catheter-related bacteremia and well as bacteremia without an identifiable focus and the whole concept of how to really utilize data from bacteremic patients in order to analyze and supplement clinical-trials data since there were really no clinical trials directly developed with protocols to look at bacteremia

specifically.

(Slide.)

Regarding the issue of bacteremia as an indication, the committee reaffirmed, again, using the concept of site-specific labeling for secondary bacteremias but also had some discussion about the concept of a primary bacteremia as a potential new indication and a fair amount of discussion focusing, again, on catheter-related blood-stream infections, catheter-related blood-stream bacteremias as a focus for future studies and potentially an area for future drug development.

(Slide.)

To give some follow up regarding the committee's thoughts on catheter-related blood-stream infections, the issues, again, of the increased incidence of those types of infections that were noted, the problems of growing antimicrobial resistance and also the limited antimicrobial armamentarium that would be available for treatment, but also the lack of the controlled clinical trials for drug development for agents to

treat path-related blood-stream infections.

There were a number of topics that were discussed including issues of what types of criteria should there be for catheter removal, what types of both clinical and microbiologic criteria should be considered, the number and the source of blood cultures for this potential indication as well as what types of laboratory studies might be considered to verify concordance of blood culture and catheter culture isolates such as DNA subtyping was discussed for Staphylococcus epidermidis.

(Slide.)

So, following the Anti-Infective Drug Advisory Committee meeting in '98, a working group was formulated at FDA, the CRBSI Working Group, and a draft guidance was developed regarding drug development for catheter-related blood-stream infections. This guidance was then presented the following year at the 1999 Anti-Infective Drug Advisory Committee meeting.

(Slide.)

There was extensive discussion about the

draft guidance and a number of issues were mentioned. I just wanted to point out some of these discussion issues because I think they are very pertinent to today's discussion and a number of them are, as yet, undefined and not clearly resolved.

Number one was the issue of a heterogenous patient population, again the concept that, looking at catheter-related blood-stream infections you would potentially be looking at a large population of patients, different types of underlying diseases, different types of catheters, tunnel/non-tunnel, short-term/long-term, and a whole variety of potentially causative microorganisms.

Number two was the sample size that might be required. Again, the thought was it may require a number of patients to screen to actually identify those who were felt to have a catheter-related blood-stream infection. In particular, there were concerns, and in studies such as this, it would be important to get catheter data, if catheters are

indwelling in the patient and what is more frequently done is they are just pulled and discarded without being cultured, the lack of catheter data may be a limiting finding.

The other issue is the concept of doing microbiologic evaluation and test-of-cure; is it necessary, what situations would it be necessary and would the lack of test-of-cure microdata, again, limit evaluation of this type of a study.

There were also concerns about the lack of a standardized disease definition for catheter-related blood-stream infection and also the lack of demonstrable treatment effect for certain types of organisms, especially organisms that are low virulence that are associated with skin sites such as coag-negative Staph, Bacillus, Corynebacterium, some of those types of bacteria.

(Slide.)

Another main area was the lack of standardized procedures as to how to manage an infected catheter. It was recognized that there was basically a lack of standard criteria to

provide proof of a catheter infection, should the types of cultures be catheter-drawn and peripherally blood-drawn blood cultures, should it be based on two blood cultures, should it be based on quantitative catheter tips, hub cultures. A number of different options were discussed without any apparent consensus.

The other issue is, in management, what would be the criteria to remove the catheter since it was recognized that patients can have different types of catheters that can be in for different periods of time and also you can have different infecting microorganisms as there was some discussion of organisms such as Staphylococcus epidermidis that may not always require removal of the catheter. Again, what types of criteria should be thought about in trying to address the catheter-removal issue.

(Slide.)

Last, microbiological issues that were discussed and I alluded to these a little bit. Number one, the issue of quantitative blood

cultures and the fact that they are rather limited in their availability. Most hospitals are not able to do quantitative blood cultures and what would be some other options to take a look at. One that was mentioned was the possibility of looking at differential blood-culture time-to-positivity.

Again, concordance of catheter and blood-culture isolates, what type of catheter-related isolates would be felt to be valid and how would it be possible to document that there would be concordance and, again, certain types of coagulase-negative Staph would probably be organisms where that would be an important issue.

As I alluded to previously the concept of test-of-cure blood cultures; do you need to do a test-of-cure blood culture in someone who studied in the context of the clinical trial for a catheter-related blood-stream infection. If the patient is well and stable and doing fine, is that really a requirement or should it be reserved basically as a secondary endpoint for patients where the catheter is retained and they are

basically treated through.

(Slide.)

So, in summary, I have tried to summarize for you the regulatory history of bacteremia and some of the early developmental history regarding catheter-related blood-stream infections. I have tried to hit on some points such as the revisions and the changes that have occurred in terminology that has been used in labeling, the Points to Consider document which has the label-indication concept as basically what is employed currently and some of the multiple issues that have been discussed at previous Anti-Infective Drug Advisory Committees in attempting to discuss and grapple with a lot of the issues about how to study bacteremia, catheter-related infections and what some of the appropriate criteria will be.

This afternoon, Dr. Janice Pohlman is going to provide some additional historical and current perspectives on catheter-related blood-stream infections, in much greater detail provide more recent information to you.

Thank you for your attention.

DR. LEGGETT: Thank you, Dr. Sorbello.

Questions from Committee

Does anyone have any questions? Don?

DR. PORETZ: I imagine that the majority of these patients are hospitalized but not all of them. There are certainly plenty of patients who have cultures obtained on an outpatient basis and are treated on an outpatient basis. But, if a patient is in the hospital, when they are discharged, the diagnoses are put on the front of the chart and coded. Is that information accurate many times and who has access to that information, and when you are trying to figure out the total number of these patients, is there a central way that information is gathered? Can you explain that me?

DR. SORBELLO: I don't know that there would be a central clearing house or anything for that type of information.

DR. PORETZ: Does anyone know?

DR. SORBELLO: I don't know.

DR. POWERS: Are you asking about ICD9 codes and their use in diagnosis?

DR. PORETZ: Yes, essentially. Where does that information--does it get entered somewhere?

DR. POWERS: In terms of for us to use, the FDA to use?

DR. PORETZ: Central reporting group.

DR. POWERS: No; we have actually gone--Janice, you may want to add to this, but we have actually had to go and actually pay to get that data from people like large HMOs and other folks to be able to actually collate that information. However, the CDC has done some studies on the accuracy or lack of accuracy with some of these diagnoses.

The probably with ICD9 codes is they are used for billing and people often code them in terms of the highest amount that they can bill for so that the accuracy sometimes is not 100 percent, certainly not to the level, the specificity, we would like in terms of enrolling people in a clinical trial.

Janice, do you want to add something?

DR. POHLMAN: You know, I did look into this and was going to speak to this a little bit in the afternoon, but I think largely the numbers that are in the literature, you know, you get this wide range--I tried to look for the ICD9 codes or, I guess, we are heading towards ICD10. It is really hard to--they are not coded specifically for that. A lot of the numbers come from nosocomial surveillance systems that actually may miss patients that are treated in an outpatient arena as some of these patients don't even get hospitalized when the bacteremia is discovered as well as patients that--some of the surveillance systems will just pick up--it depends on how the hospital is doing surveillance on whether or not they are doing non-critical-care units. It may just be they are getting critical-care numbers so the estimates are really subject to a lot of variation.

DR. LEGGETT: Alan?

DR. CROSS: At one point, the arguments in the infectious-disease community were really on,

for example, the length of therapy for Staph aureus bacteremia based on whether or not there was either a non-removable or removable focus. It sounds like, going through your discussion, that really was never a viable discussion.

I think if one thinks back on that type of discussion, obviously catheter-related infections would be a subset of removable foci. On the other hand, the nonremovable focus would encompass Staph aureus bacteremia of a multitude of primary foci, whether it was from the skin, the urine or elsewhere.

That has never entered into any of the discussions, it sounds like.

DR. SORBELLO: There had been some discussions about treatment although there was not a great focus on duration of treatment. I think part of that was because of the discussion about how do you really manage the catheter? Who do you identify and can you identify some type of uniform guidelines of who has a catheter removed, what kind of catheters remain; is it related to the type of

organism; do you treat them differently if you keep the catheter in versus you take the catheter out.

So it had been discussed but I think it was kind of folded into some of the other more structural constructs of how to really go about formulating some type of, if you could, a uniform management guideline for catheters.

DR. CROSS: But, looking at the other end of it, though, of the nonremovable foci, it sounds like a discussion of the origin of the bacteremia seemed to make a difference in terms of the recommendations. I don't know whether there is any data presented at those meetings to actually support that point of view.

DR. SORBELLO: Not specific data that I remember from the transcripts but, again, the previous Anti-Infective Drug Advisory Committees felt, overall, that going with site-specific indications and then tying the terminology of bacteremia to an identifiable focus was most appropriate for labeling.

I think part of grappling with

catheter-related infections was there was really no standardized uniform accepted definition of what a catheter-related infection was let alone best management because everybody has somewhat of a different way to kind of tailor their approach, again depending on the organism, the type of catheter, the type of patient.

So I think treatment is an extremely important aspect of all this and I think it really folds in as a very important aspect of management. But I think some of the other constructs of actually how to put the clinical trial together and develop a population appeared to be somewhat more of a priority in the prior discussions.

DR. LEGGETT: It has also been a moving target looking at the new drugs we have looked at that are treating five days for pneumonia, et cetera.

Chris?

DR. OHL: Could you outline how the discussions went parallel to all of--in this time line related to endocarditis and diagnosis of

endocarditis for trials?

DR. SORBELLO: Actually, there was not much discussed regarding endocarditis at the prior Anti-Infective Drug Advisory Committee meetings as far as criteria for a clinical trial, criteria for labeling. There was not really an in-depth discussion about that.

As I say, the '93 Anti-Infective Drug Advisory Committee meeting was basically grappling with the new definitions that were published of how do you define what sepsis is, how do you fit that in to the clinical setting and how do you tie that in, then, to the labeled indications that were used at the time which were bacteremia and septicemia where there was still a lot of confusion and discussion about whether they are specific enough and appropriate enough for a label.

But there was not really an in-depth discussion about endocarditis as an indication.

DR. LEGGETT: Jan?

DR. PATTERSON: I wonder if you could clarify for me what we mean when we say primary

bacteremia because, as a hospital epidemiologist, in doing nosocomial infection surveillance, when we look for catheter-related infections, we want to make sure that there is not another identifiable site so that it is not a secondary infection.

So we call it a catheter-related infection and sometimes we even use the term primary bacteremia. With Staph aureus, as clinicians, we very often find a source, whether it is endocarditis or an abscess or the catheter. So I am just wondering if you could clarify for me what we mean by primary bacteremia versus catheter-related.

DR. SORBELLO: The context that those terms were used in the historical setting was the primary bacteremia either referred to the patient with endocarditis or the catheter-related infection and that bacteremias, secondary bacteremias, were where you had some other identifiable focus, whether it was along with the urinary tract or whatever.

But primary bacteremia in the historical

sense here was used either in the setting of endocarditis or catheter-related.

DR. LEGGETT: Barth?

DR. RELLER: I have had the great privilege of actually, I think, being at every one of the meetings that Dr. Sorbello--and the comment that I wanted to make was that he has done a masterful and accurate capture of the essence of that decade.

I think history is very important if we are to learn from it. And a few additions. Dr. Cross brought up the question of role of removal. In fact, that has been discussed because--not that the answers are in, but the discussion, because the recognition that removal is of varying degrees of facility in importance in the outcome but must be considered and that was captured here; that is, whether it is a peripheral catheter, indwelling, tunneled, et cetera, and also the organism and the interplay between the organism so that a catheter that has Candida or Bacillus or a coagulase-negative Staph, the actions may be quite

different based on recognized outcome.

Dr. Ohl's query about endocarditis; one of the hesitancies, the caution, about an indication for catheter-associated bacteremia or that the organism makes a huge difference and the recognition that particularly--not exclusively but particularly--with Staph aureus, the specter of endocarditis which is a segue to Dr. Patterson's comment of usually finding a source if the source is endocarditis but also grappling with the reality that I am sure will be more discussion today when there is Staphylococcal bacteremia, is the source endocarditis or is endocarditis a consequence, one of the many consequences, of the bacteremia regardless of what the initiating source was.

So one gets into a chicken-egg phenomenon and the organism, the source, the relative role of removal, the kind of intervention, drainage, removal, extirpation in terms of valve replacement, that these things are incredibly complicated.

Again, for starting points, as Dr. Sorbello said, I mean it is a very complicated

history but it is a complicated topic and he has really captured the main points. Some of these other things that have come up, it is not that they were ignored during the time but it is one of the reasons that the end conclusions were reached at the different points sequentially because, clearly, the patient population and the options have also evolved, I mean whether the patient is granulocytopenic and the chemotherapy and the kinds of catheters and the spectrum or organisms and the resistance mechanism--I mean, it is a very different world in 2004 from 1992.

The last thing, very briefly, is I was not in second grade in 1965 like Janice Soreth. On the other hand, I was not on the committee in 1965. (Laughter.)

DR. LEGGETT: Tom and then John and then, unless there is anything really urgent, let's move on.

DR. FLEMING: Fred, back on your Slide 12, I had a follow-up question that was related to Jan's question. Basically, on Slide 12 is you are

referring to catheter-related BSI. You have noted in that second-to-the-last point that we have got catheter-related bacteremia and bacteremia with unknown source.

It is my understanding that your guidance document for CRBSI focuses exclusively on the former while, when we are going to go on this afternoon and talk about PBSA, will be inclusive to both. Is that correct?

DR. SORBELLO: Yes, because there was discussion, actually, at the '98 Anti-Infective Drug Advisory Committee as to whether some proportion of the patients who have an unidentifiable focus but have catheters in place could actually have been catheter-related. So there was a fair amount of discussion about that and how to really view them and how to consider them within the total spectrum.

DR. LEGGETT: John?

DR. BRADLEY: In stepping back for a moment and looking at some of the questions that Dr. Soreth had asked at the very beginning, in

trying to get a protocol with inclusion and exclusion criteria that will work, the whole issue of the patient who has a fever and looks bacteremic is one that I think is an even more important issue than drilling down to how many blood cultures because that defines a small sub-segment of those who look bacteremic.

Rule out sepsis is a very common admitting diagnosis in pediatrics, certainly, and probably in the adult world as well so, to me, one of the biggest hurdles is to try and figure out empiric therapy for bacteremic disease, suspect bacteremic disease, and then contrast that with how we are going to define the treatment, the drugs, the duration, for documented infection whether it be with the catheter in, with the catheter out, with endocarditis, without endocarditis.

So the approach to empiric therapy, to the septic patient, I think, is a huge program and, in the April of 2004 hearing, the details of one of the pharmaceutical companies trying to study this, it is clear that we need to further define what

empiric operational definitions we can use so that we can enrich for evaluable patients.

The critical-care community with I.D. and pulmonary and surgical help made the first attempt to define SIRS and the septic patient. They were unhappy with their definitions. They are in the process of redefining them. Three weeks ago in Boston, a group of us got together to try and redefine what is the septic patient because they all look septic. You just don't know which ones are actually infected or not.

As you had said, Jim, it is a moving target so those definitions from 1992 have been changed for adults. We are changing them for kids. We are not the only ones that want to study the septic patient. There are biologics, pressers, all sorts of other people who are with us in trying to get our arms around what is this patient and what is the underlying process and how can we study it.

DR. LEGGETT: Celia?

DR. MAXWELL: Just one brief question on Slide 16. While I know that a large sample-size

requirement would be an issue, was there any speculation as to what kind of a sample size you would need to begin to answer the question?

DR. SORBELLO: An actual numerical sample size was not something that was directly discussed, but I think the core issue really regarding sample size is how do you define a catheter-related blood-stream infection, what criteria do you need to make that identification and, again, if you are dealing with a clinical study where there may not be uniformity in capturing catheter data because catheters are pulled and discarded without being cultured or there are not exit-site cultures done, et cetera, you are losing a major piece of information, at least microbiologic information, that is needed to properly do the study.

So I think the size of the sample really dovetails with how you define it and what your criteria are to prove it, that it actually is a catheter-related blood-stream infection. I think that tends to restrict the number of patients that can be enrolled because there are some rather

strict microbiologic data that needs to be collected to do that.

DR. LEGGETT: Thank you, Dr. Sorbello.

Janice, before we go on?

DR. SORETH: Just a quick comment to follow up on Celia's point. I think we are going to hear more about this from the companies who are going to speak in the Open Public Hearing setting with regard to their experience with trying to do the trial, the number of patients screened versus the number of patients evaluable as it is, no pun intended, a sticking point for catheter-related blood-stream-infection trials.

DR. LEGGETT: We are now going to hear from Dr. Nambiar who is going to talk to us about the epidemiology of Staph aureus bacteremia.

Epidemiology of Staph aureus Bacteremia

DR. NAMBIAR: Thank you, Dr. Leggett and good morning everybody.

(Slide.)

In the next twenty minutes or so I will briefly discuss some salient epidemiology

characteristics of Staph aureus bacteremia. The clinical implications of this cumulative epidemiologic evidence as it relates to clinical-trial design will be discussed by Dr. John Powers in a subsequent presentation.

(Slide.)

Although staphylococci were first described about 125 years ago by Sir Alexander Ogston, it continues to evoke immense interest and respect among members of the medical community both because of its tendency to cause severe disease and its tendency to develop resistance to antimicrobials.

(Slide.)

Staph aureus is an important cause of bacteremia in hospitals both within and outside the United States. Data from the SCOPE project from 1995 to 1998 showed that Staph aureus was the second-most common blood-stream isolate and it caused 16 percent of all hospital-acquired bacteremias.

Data from pediatric institutions over a

slightly longer time period showed that Staph aureus caused 9 percent of all hospital-acquired bacteremias. In a seven-year study from a single institution in Switzerland which was an acute-care facility, it was noted that 14 percent of all bacteremias were caused by Staph aureus.

Limited data is available on the incidence of community-acquired Staph aureus bacteremia. In a study from four metropolitan areas in Connecticut in 1998, it was noted that the incidence of community-acquired Staph aureus bacteremia was about 17 per 100,000 persons.

(Slide.)

The increasing incident of Staph aureus bacteremia is paralleled by an increase in the incident of infective endocarditis due to Staph aureus. About 25 to 40 percent of native value endocarditis is now caused by Staph aureus. In a series of 329 patients with infective endocarditis from a tertiary-care facility, 40 percent of all endocarditis was caused by Staph aureus and the frequency of infective endocarditis due to Staph

aureus increased from 10 percent in 1993 to 68 percent in 1999.

(Slide.)

Why is Staph aureus bacteremia different from other causes of bacteremia? It can present with a wide spectrum of clinical manifestations ranging from uncomplicated bacteremia to severe fulminant and often fatal disease. Complications are common and are often difficult to identify or to predict.

Given its protein manifestations, it is difficult to standardize the extent of diagnostic procedures. There is significant overlap of infective endocarditis and the two are often difficult to differentiate clinically. Mortality from this disease remains high. Additionally, it poses there issues both related to its development of resistance to common antimicrobials and uncertainty regarding the optimum length of therapy.

(Slide.)

The common risk factors identified for

Staph aureus bacteremia include the use of intravascular catheters, hemodialysis, intravenous drug use and the presence of underlying illnesses such as diabetes mellitus and immunosuppression.

(Slide.)

Staph aureus bacteremia has been classified several different ways in the literature. It can be classified as community- or hospital-acquired. It is classified as primary or secondary depending on the absence or presence of an apparent primary focus of infection. It is classified as complicated versus uncomplicated depending on the presence or absence of certain clinical characteristics.

(Slide.)

Although all patients with Staph aureus bacteremia necessarily have a focus of infection, it is not always apparent. How often there is an obvious focus of infection depends upon the series of investigations performed, the presence or absence of an intravascular catheter, whether the population consisted primarily or intravenous drug

uses versus non-drug uses, whether the disease was acquired in the community or in the hospital.

On an average, there is no obvious focus of infection in about 20 percent of cases.

(Slide.)

This is a graph I have taken from a recent paper by Jensen describing the importance of focus identification in patients with Staph aureus bacteremia. The line in red represents how often an unknown focus was reported. This is data compiled from 14 published studies. The line in blue depicts how often intravascular catheter was reported as the focus of infection.

So, in the '90s, the two cross and the frequency of an unknown focus being reported has significantly decreased while that due to intravascular catheters is on the rise.

(Slide.)

In 1976, Nolan and Beaty reported in a retrospective study of 105 cases with Staph aureus bacteremia. This is one of the earlier descriptions of two fairly distinct clinical

populations, the first group consisting of 63 patients, all of whom had an apparent primary focus in infection. These patients were more likely to have hospital-acquired disease. They tended to be older with a mean age of 55 years. They were more likely to have significant underlying illnesses. Secondary foci were less likely and only two out of the 26 patients with infective endocarditis belonged to this group.

In the second group of patients, none of them had an apparent primary focus of infection. They were more likely to have community-acquired disease. They were younger with a mean age of 37 years. They were more likely to use intravenous drugs, more likely to have secondary foci and 24 out of the 26 cases of infective endocarditis belonged to this group.

(Slide.)

Subsequent studies have also documented that patients with community-acquired Staph aureus bacteremia are more likely to have an unknown portal of entry, more likely to develop metastatic

disease and have a poorer prognosis. All of these most likely reflect the fact that medical attention is sought later probably after the onset of bacteremia and before the institution of effective therapy.

How often Staph aureus bacteremia is community-acquired differs between studies essentially because of differences in definition. Most investigators would classify it to be community-acquired if a positive culture developed within 48 hours of admission to the hospital. However, other investigators have used longer cutoffs of 72 to 96 hours.

Using a 48-hour cutoff to define community-acquired disease, Jensen, et al., in their series of 278 cases of Staph aureus bacteremia from Denmark noted that just under 50 percent had community-acquired disease.

Another important factor to consider in the definition of community-acquired Staph aureus bacteremia is if there was any prior contact with the healthcare system. In the series by Morin, et

al., from Connecticut that I referred to earlier, 192 patients had community-acquired disease and 62 percent of them had some prior healthcare contact.

(Slide.)

Staph aureus bacteremia is classified as complicated versus uncomplicated by different investigators using various definitions. Some authors would classify it as complicated if a focus of infection was not identified or it was non-removable while others would classify complicated Staph aureus bacteremia if there was evidence of metastatic disease, deep-seated infections or other complications such as acute respiratory-distress syndrome, or DIC.

In a series of 724 cases described from Duke University Medical Center, complicated Staph aureus bacteremia was defined as the presence of attributable mortality, evidence of infection extension or metastasis, embolic stroke or recurrent Staph aureus infection within the 12-week follow-up period.

The authors noted the following four risk

factors to predict the presence of complicated Staph aureus bacteremia; a positive blood culture at 48 to 98 hours later; community-acquired disease; skin findings such as petechia or vasculitis suggesting acute systemic infection; and persistent fever at 72 hours.

(Slide.)

We have already heard some discussion about Staph aureus bacteremia and catheters and, needless to say, it is very controversial. Reports of increasing association of catheters and Staph aureus bacteremia pertain both to hospital-acquired and community-acquired disease and the increasing association with community-acquired disease may just be a reflection of changing medical practices.

As with everything else I have presented so far, the definitions, really, vary between studies. By and large, catheter is usually considered the focus of infection if there is no evidence of an alternate source and there is evidence of inflammation or infection at the catheter-insertion site or a catheter-tip culture

is positive for Staph aureus.

However, in the absence of catheter microbiologic data, either because the catheter was not removed or the catheter was not cultured, it is often a diagnosis of exclusion.

(Slide.)

Steinberg, et al. reported on the association between catheters and Staph aureus bacteremia over two time periods from Atlanta. In the first time period, from 1980 to 1983, they noted that 25 percent of all hospital-acquired Staph aureus bacteremia were related to the use of intravascular devices. There were no documented catheter-related community-acquired Staph aureus bacteremia during this time period.

However, from 1990 to 1993, they noted that 56 percent of all hospital-acquired Staph aureus bacteremia and 22 percent of community-acquired Staph aureus bacteremia were associated with intravascular devices.

In a larger series of patients, again from Duke University Medical Center, it was noted that

about 50 percent of patients with Staph aureus bacteremia had an intravenous catheter as the focus of infection.

(Slide.)

The incidence of infective endocarditis in patients with Staph aureus bacteremia were really depending upon the patient population studied and the extent of evaluation performed.

Traditionally, the following three bedside criteria, as proposed by Nolan and Beaty, in 1976 were used to predict to presence of infective endocarditis in patients with Staph aureus bacteremia, community-acquired disease, the absence of a primary focus of infection and evidence of metastatic disease. However, subsequent studies have shown that infective endocarditis can occur in patients with hospital-acquired disease. It can occur in patients who have an obvious primary focus of infection and can occur in a population of non-drug users.

In a series of 59 patients with Staph aureus infective endocarditis, Fowler, et al.,

reported that 46 percent, in fact, had hospital-acquired disease. In a series of 76 patients with Staph aureus bacteremia all of whom were non-I.V.-drug users 59 had an obvious portal of entry and 13 of these 59 patients had evidence of infective endocarditis.

(Slide.)

Infective endocarditis is often missed based on clinical findings alone. In a ten-year study from Denmark, it was noted that endocarditis was missed clinically in over half of the 152 pathologically confirmed infective endocarditis due to Staph aureus.

In a prospective series of 103 patients with Staph aureus bacteremia that was studied, 26 were noted to have infective endocarditis using the Duke criteria. Clinical evidence was, however, seen in only seven patients, five of whom had peripheral emboli and two had new murmurs. Transesophageal echocardiogram identified vegetations in 22 patients, abscess in two, perforation and new regurgitation in one each.

(Slide.)

Risk factors for Staph aureus infective endocarditis include the presence of native value disease which historically was associated with rheumatic heart disease. However, structural abnormalities such as mitral-valve prolapse, degenerative disease such as aortic-valve sclerosis and congenital heart disease also predispose to development of infective endocarditis.

Other risk factors include the presence of a prosthetic valve, history of intravenous drug use or prior infective endocarditis and community-acquired disease.

(Slide.)

How often patients with Staph aureus bacteremia will develop metastatic disease again varies between studies. On average, about a third of patients will develop one or more metastatic foci. In a retrospective study of 281 patients with Staph aureus bacteremia from Switzerland, 27 percent developed metastatic disease. Common sites included the joints, kidneys, nervous system, skin

and intervertebral disc. Half the patients had more than one metastatic focus of infection.

In a more recent prospective study of 68 patients published in 2000 by Ringberg, et al., and this was very appropriately titled "To Seek is to Find." They noted that 53 percent of patients, in fact, had evidence of metastatic foci. Patients underwent a fairly extensive evaluation including one or more of the following; X-rays, echocardiogram, bone or leukocyte scintigraphy.

(Slide.)

Risk factors for metastatic disease include community-acquired bacteremia, primary Staph aureus bacteremia, presence of prosthetic devices including orthopedic devices, implantable pacemakers and defibrillators. The study also suggested that persistent bacteremia would be an important risk factor for developing metastatic disease.

Among 104 patients with Staph aureus bacteremia, 59 percent of patients with a positive blood culture, more than 24 hours after starting

effective therapy, developed metastatic disease compared to 17 percent without sustained bacteremia.

(Slide.)

The two important issues that come up in the discussion of metastatic disease is development of metastatic disease always represent lack of drug efficacy. If not, from what time point after institution of effective therapy can we always attribute it to lack of drug efficacy. And this will come up again in the discussion by Dr. Powers later this morning.

There is some evidence in patients with infective endocarditis that suggests that once you institute effective therapy, the rate of embolic phenomenon seems to decline. So, in a retrospective study of 207 patients with left-sided infective endocarditis, it was noted that the rate of embolic events decreased from 13 per 1000 patient days during the first week of therapy to less than 1.2 per thousand patient days after completion of the second week of therapy.

However, in my review of the literature, I found there is only limited data available about inpatients with Staph aureus bacteremia regarding the time to development of metastatic disease. In a small series of patients, of 39 patients with Staph aureus bacteremia, Libman, et al., reported that nine developed metastatic complications, one within the first week and eight after the first week of positive blood culture, two of whom developed metastatic disease four weeks after institution of therapy.

(Slide.)

This has already been brought up for discussion this morning; what is the optimum length of therapy. It really depends on the extent of disease and the presence of host risk factors. Generally complicated infections such as infective endocarditis and deep-tissue abscesses need prolonged duration of therapy somewhere in the range of four to six weeks.

However, the appropriate length of therapy for patients with uncomplicated disease is still

controversial. Some investigators propose 14 days of therapy while others propose longer duration based on higher complication rates seen with shorter therapy.

(Slide.)

Acute systemic complications such as the acute respiratory distress syndrome, disseminated intravascular coagulation and septic shock usually occur within the first 48 hours. Mortality in patients with Staph aureus bacteremia in the pre-antibiotic era was as high as 82 percent as reported by Skinner and Keefer in 1942.

Currently, though, the mortality rates are much lower. They still remain fairly high, between 16 to 35 percent. Risk factors for morality include the severity of illness at onset of bacteremia, presence of an unknown source of infection, older age and noneradicable foci.

About 12 to 15 percent of patients with Staph aureus bacteremia will develop recurrent disease. Risk factors for recurrence include the presence of persistent bacteremia, a retained

intravascular device and the presence of noneradicable foci.

(Slide.)

So, in summary, these are some of the important challenges we have identified with Staph aureus bacteremia most of which have a bearing on the design and conduct of clinical trials. Clinically, it is classified several ways; community- versus hospital-acquired, primary versus secondary, complicated versus uncomplicated. Due to its overlap with infective endocarditis, there is often a need for echocardiographic evaluation.

Because of its propensity to cause metastatic disease, there is often a need for extensive diagnostic procedures and as metastatic disease always due to drug effect is still unclear. The association with intravascular catheters is sometimes based on stringent laboratory criteria but often is a diagnosis of exclusion.

Treatment issues posed with Staph aureus bacteremia include the need to initiate empiric therapy given the nature of the disease, the choice

of initial therapy which often is based upon the resistance patterns in any given institution and the uncertainty regarding the need for short versus long-course therapy.

Thank you.

DR. LEGGETT: Thank you, Dr. Nambiar.

Questions from Committee

DR. LEGGETT: Does anyone have any questions? Tom?

DR. FLEMING: I am trying to understand the sequelae for what might be, in fact, a PBSA cohort. We have seen that there are several important clinical consequences that you have referred to that are mortality, endocarditis, metastatic disease. And the evidence that you have shown, if I am understanding it, would suggest that effective antimicrobial therapies delivered sufficiently early in time could have an important benefit in reducing the metastatic-disease rates.

Is that also true for the ability to reduce the rate of I.E. and mortality and would we be able to see those effects, particularly on

mortality, by only following a moderate period of time because, as I understand from this, a lot of the mortality is, in fact, within 30 days.

DR. NAMBIAR: Even though there is some evidence to suggest that once you institute appropriate therapy, the likelihood or the risk of developing metastatic disease is decreased. I think what is not clear at this point is is there a difference if metastatic focus manifests for the first time in the first week of illness, whether it manifests in the second week or in the fourth week, especially some metastatic foci like bone infections may not be evident early on.

So what is not clear to us, and we are seeking help from the committee, is from what point on do we attribute it completely to lack of drug efficacy. The other important issue that comes up is this drug that we are going to develop to treat Staph aureus bacteremia, should it have penetration to every potential site where Staph aureus can develop a focus of infection.

DR. FLEMING: Just to follow up on that,

certainly some of these events are events that would have been seeded prior to the initiation of the antimicrobial therapy. Some, however, presumably will be prevented which I would think would be a major benefit of such therapy.

So, for infective endocarditis, is it reasonable to presume that we would be able, because of this chicken and egg--presumably some of this is, in fact, caused by Staph aureus bacteremia--is it plausible to think that, with effective therapy, we should be able to detect a reduction in the incidence cases post-therapy of I.E.?

DR. NAMBIAR: Yes, provided you have done everything to exclude I.E.

DR. FLEMING: Certainly, that would mean, and I follow you on that--that would reduce the diluting if we have done as much as we could to exclude cases that are already preexistent.

DR. NAMBIAR: I think, in my understanding, that would be a fair assumption.

DR. LEGGETT: Tom, there is the other

problem of effective treatment and losing, nonetheless, because a good proportion of folks who have endocarditis lose their valve four to six weeks into therapy when cultures are sterile. So that just further complicates that.

Jan?

DR. PATTERSON: It was a nice review. I just wanted to comment that since that Jensen review, there has been the emerging problem of community MRSA which has affected the rate of community Staph aureus in general. Indeed, it does appear to be a different epidemiology in terms of the invasiveness of the infection and the fact that people may even stay bacteremic on bactericidal therapy for Staph aureus.

So, probably, it is with the PBL talks that those particular strains have--that would probably be considered a risk factor, I think, for morbidity and mortality as well.

DR. LEGGETT: As well as an incentive for drug companies to produce new drugs.

Joan?

DR. HILTON: It seems to me that, in trying to decide whether a therapy is effective, it would be great if there is time to evaluate a patient's baseline status, then treat, then evaluate the effective therapy. I am wondering if there are patients in whom there is not time to evaluate that baseline status that it is imperative that you start therapy right away.

If there might be a different group of patients in whom you actually can take a number of days or whatever time is needed prior to starting therapy, I think this leads into clinical-trial design.

DR. NAMBIAR: I think that would be an issue because I think, given the nature of the beast, I don't think we have the luxury of waiting for a few days before you actually initiate therapy. In fact, you are more likely to have a situation where most patients would have received some empiric therapy, I think like the example Dr. Leggett said. All that you would know is that there are Gram-positive cocci in clusters.

If you all those risk factors, you are going to assume it is Staph aureus and, more than likely, I, as a clinician, wouldn't hold back treatment. So I think having the luxury of waiting for some time and then evaluating the patient--and, again, the other issue that comes up is how much evaluation is good enough. Do you subject every patient to every test that is known because this particular organism has a propensity to seed in multiple sites.

So I think part of it is going to be a clinical judgment issue because I think it is hard to mandate that every patient be subjected to every radiologic procedure available to detect a potential occult focus.

DR. LEGGETT: Certainly expensive. Joan, I think part of the problem is we are trying to get at a final common pathway, final common denominator, and there are multiple ways to go there. So we oftentimes tell our residents to sit tight and don't start antibiotics until you know what is going on.

But then there are the other people who are deathly ill that we start right away.

Don?

DR. PORETZ: Just in answer to your question, also, there are significant medical-legal questions because I have reviewed multiple files and, if you suspect a bacteremia and you don't act on it, and a patient is bacteremic, the medical-legal repercussions are very, very significant.

DR. LEGGETT: As long as the outcome is bad.

John?

DR. BRADLEY: I was going to mention, as Jan did, that, as we move forward, looking at PVL-positive community-acquired MRSA is going to be incredibly important because the disease is firmly within pediatrics right now and at the IDSA meetings a week or two ago, the warning was put out that children get it first and watch out, adults; you are next.

The other issue that had to do with

waiting to start antibiotics, it is the standard of care right now in a child who has fever to start antibiotics while your blood cultures are pending. In order to go through a human research committee to present to a parent, mother or father, that we are withholding antibiotics and the potential complications is death I don't think would go over very well.

DR. LEGGETT: Chris?

DR. OHL: Just one other comment to add on that. I think that we are also discovering that Staph aureus in its resistance has become somewhat heterogeneous. More difficult to predict what and whom might respond to therapy that would thought to be sufficient based on microbiological MIC data. We are still learning on this issue and it will be some time before that comes to fruition.

DR. LEGGETT: Thank you, Dr. Nambiar. If there are no further questions, we will move on.

Dr. Patrick Murray is now going to talk to us about Microbiological Considerations in Diagnosing Staph aureus Bacteremia.

Dr. Murray?

Microbiological Considerations in Diagnosing Staph aureus Bacteremia

DR. MURRAY: Thank you.

(Slide.)

John Powers asked me if I would give an overview of the microbiology of the issues that we are discussing today. I notice we are running a few minutes overtime. Hopefully, I won't exacerbate that problem. I think that I would be able to cover this material within the allotted 20 minutes or so.

(Slide.)

What I am going to do is divide my presentation into three components. I will start off with an overview of the blood-culture systems and I think the theme that I want to get across in that portion of the presentation is that not all negative cultures are created equally. We tend to think that a negative culture means really there are no bacteria there. I think what I can do, when I finish this presentation, is emphasize where, in

fact, we can go wrong and miss the opportunity to detect organisms in the bloodstream.

I will then talk a little bit about interpretation of the culture results and then, finally, the last maybe half of the presentation will be on identification of staphylococci, both the traditional methods for identifying the staphylococci as well as the newer genetic approaches to this.

(Slide.)

If we start off with an overview of blood-culture systems, the first thing that we have to do is collect an uncontaminated blood sample. Skin antisepsis is pretty well defined, what should be done. The surface to the skin should be cleaned with 70 percent alcohol. It should be allowed to dry, air dry. Then that is followed by either a 2 percent tincture of iodine, povidone iodine, or chlorhexadine.

Of the three disinfectants that I just mentioned, the povidone iodine which is traditionally the disinfectant that has been used

most commonly is probably the least effective and that is because it needs to be on the skin surface for about two minutes for it to kill the bacteremia that are there.

2 percent tincture of iodine or chlorhexadine both work much faster and, for that sense, it is probably more effective at least based on traditional practices.

The other question that could be raised is what is considered an acceptable rate of contaminated blood cultures. I would say that there is no acceptable rate. We don't want to have contaminated blood cultures. But, generally, the goal of institutions is to keep the contamination rate below 3 percent.

In my experience, what we find is that, although you may have a rate of less than 3 percent, in certain parts of the hospital, you may have much higher rates. Emergency departments is a good example of that where the contamination rate can be much higher.

I think in any sort of a program for

reducing contaminated blood cultures, it is important for the institutions to know where their problems are and address those specifically.

The volume of blood is the most important aspect of collecting a successful blood culture. Most septic patients have less than 1 organism per milliliter of blood, whether that be bacteremia or fungi, that theme applies. So the more blood you collect, the greater the chance of getting a positive blood culture. There have been a number of studies that have looked at that.

Those studies, then, form the foundation for the current recommendations that, for an adult patient between 20 to 30 milliliters of blood should be collected for each blood culture and that volume of blood is divided into two or three bottles. For children and for infants, there is proportionately less blood that would be collected.

The dilution of blood in the broth is also important. The minimum dilution is a 1 to 5 ratio between the blood to the broth that is in the culture systems. Now, there are resin media that

are available that allow you to have a more concentrated amount of blood in the broth. I tend to think that that is not a good practice. I think what we want to do is maximize the amount of growth medium that is available to support the growth of the organisms.

The number and timing of cultures really depends on the type of--I am almost afraid to use the term bacteremia or septicemia right now, so I will use it in a more generic sense of bacteremia. The number and timing is really dependent on the type of infection. If it is a continuous infection, and that would be an intravascular infection like an infection localized on the heart valve or on a catheter, then, really, the timing is not critical because the bacteremia will always be present in the bloodstream.

The key, then, is to collect enough blood to detect to organisms that are there. On the other hand, if it is a localized focus, say, a lung or urinary tract or an abscess, then we would expect that, for many of those patients, you are

going to have intermittent spillage of organisms into the blood and so the timing becomes critical and the number of cultures that are collected becomes critical.

The recommendations are that two to three blood cultures should be collected within a 24-hour period of time. Additional blood cultures really are not terribly useful unless you are looking for specific fastidious organisms.

The methods that we use to culture bacteria and fungi in the blood have evolved over a number of years. The manual methods, which consisted of bottles of nutrient media, really have been replaced by automated methods today. I think there are very few laboratories that would have a manual method where they would inoculate the bottles and then periodically look at the bottles to see if there is evidence of microbial growth in those bottles.

The lysis centrifugation system is a technique where you draw blood into a vacuum tube. It has a lysine reagent in the tube which lyses

the blood cells. You concentrate the organisms by centrifugation and then you take the pellet and you inoculate solid media with that. The advantage of that system is that you can do a quantitative blood culture.

The disadvantage is the lysine solution can lyse some organisms that you are interested in. Staphylococcus pneumoniae is a good example of that. In addition, there is a higher incidence of contamination of those cultures because of the manipulations.

Most laboratories today use an automated method for processing blood cultures. There are three major players on the market today in the United States. Each of them are detecting growth or organisms by the metastatic activity of those organisms and that could be the production of carbon dioxide, the consumption of oxygen, and both of those can be detected by sensors or it could be detected by changes in pressure within the bottles.

Those systems are comparable. There are subtle differences between them, or among them. I

think each laboratory has their preference in what they would like to use but I would say all of those are superior to the manual methods that existed before.

(Slide.)

If we look at the interpretation of the culture results, the first is the time to detect the positive culture. I could say that most positive cultures, probably 90 percent of more of the positive cultures that are detected in the laboratory are detected within the first 48 hours of incubation. That is one of the advantages of the automated systems. The manual systems took longer in order to detect a positive culture.

Organisms like Staph aureus, the Enterobacteriaceae, betahemolytic streptococci, all of those will grow generally within the first 24 hours of incubation. In contrast, organisms like the coagulase-negative staphylococci can take more than 24 hours on the average before you detect their growth.

So one way of separating those organisms

just within the laboratory is that if it grows quickly and it looks like a staphylococcus there is a greater chance that that is going to be Staph aureus compared with the other staphylococci.

Cultures are routinely held in laboratories five to seven days. There are some laboratories that hold bottles for a shorter period of time. I think that does compromise their success in isolating some organisms, particularly on patients that have been started on antibiotics before the blood cultures were collected from those patients.

Extension beyond seven days is generally unnecessary unless you are looking for more fastidious organisms such as those that may cause subacute bacterial endocarditis.

The spectrum of organisms recovered blood cultures, this has been touched on already in one of the earlier presentations; about 10 to 15 percent of blood-culture bottles--blood cultures--are going to be positive, and they can be positive in one or both bottles that would be

inoculated.

The most common isolates are the coagulase-negative staphylococci, Staphylococcus aureus, Escherichia coli, the Enterococci, Klebsiella and Streptococcus pneumoniae and probably in that order, although that does vary from hospital to hospital depending on your patient population.

The key point, though, is the most common organism that we will see in the laboratory will be the coagulase-negative staphylococci. Most isolates of Staph aureus, Streptococcus pneumoniae, the beta-hemolytic streptococci, Enterococci, Enterobacteriaceae, Pseudomonas, the Gram-negative anaerobes and yeast are going to be significant. So, if we see those in the blood culture, generally that is a significant finding.

In contrast, most isolates of the coagulase-negative staphylococci, Corynebacterium, Propionibacterium and Bacillus are clinically insignificant. Each of those are organisms that can colonize the skin surface and contaminate blood

cultures.

So the important point that I would make there is that the coagulase-negative staphylococci are the most common organisms we see and also are commonly insignificant. In contrast, Staph aureus is the most common significant organism that we see but it is--again, we have to be able to differentiate that from the coagulase-negative staphylococci.

The other point that I would make is that the coagulase-negative staphylococci do cause significant infections but almost always they are associated with either a contaminated line or another foreign body that is present in the patient such as the prosthetic heart valve, prosthetic joint and so forth.

(Slide.)

Identification of staphylococci has evolved over the years and I think, in the last three or four years, we are getting more sophisticated and I think, also, offer opportunities here to help with some of the issues

that are under discussion today.

What I would like to do, though, is to mention that, for blood cultures, the way we approach identifying organisms is different from how we do with other types of cultures. Other cultures traditionally we are going to have the organisms isolated on a plate. We can pick the colonies, set up the biochemical test and be able to identify the organisms.

Because, in blood cultures, there are so few organisms in the patient's blood, we are forced to inoculate the blood into a large volume of broth and grow the organisms initially in that manner. So what we are faced with, then, is a bottle with 50 to 100 milliliters of broth and blood with the organisms present.

Now, we can take those bottles. We can subculture them and the next day pick isolated colonies and go ahead and do identification tests, but that is going to introduce a one-day delay. So, traditionally, what most microbiology laboratories attempt to do are some rapid tests

using procedures where we can concentrate the organisms from the broth and perform our test that way.

Now, that subculture plate--traditionally, microbiologists will take a plate. They will subculture the organisms onto the plate. They put it into an incubator and they don't look at it until the next day. In fact, if you go and you take that plate after four to six hours, you can see growth is present there, growth that you can use to set up your biochemical test and identify your organisms or set up your antimicrobial susceptibility test and have the results available the next day.

Another approach would be to concentrate the organisms that are in the blood. But, again, the first approach was to use differential centrifugation, a low-speed centrifugation, to remove the erythrocytes that are present and then a high-speed centrifugation to concentrate the organism. You would take that pellet of organisms and use that to inoculate your test.

A different approach to do that is to use the serum-separator, or clot tube, which are commercially available and you centrifuge your blood in that tube. Your blood cells would be concentrated in the bottom of the tube. The organisms, either bacteria or fungi, are concentrated on the top of the plug that is there and, above that, would be the rest of the blood.

You can remove the organisms with a pipette and go ahead and set up your test from that. Now, you can also take the broth, itself, and set up tests without concentrating the organisms. The broth can be used for what I will talk about in a few minutes, the FISH test, or fluorescent in situ hybridization test, can also possibly be used with molecular probes and I will discuss that also in a few minutes.

But you need a heavier inoculum from a subculture plate or from a concentrated pellet of organisms to perform the coagulase test and the protein-A test. The coagulase test is the ability of a staphylococcus to clot plasma, a very simple

test. It has been historically used to identify Staph aureus for many, many, many years.

The recommended plasma that should be used is EDTA rabbit plasma, commercially available and readily available. The coagulase enzyme--there are actually two enzymes that we are interested in. One is bound to the surface of the bacteria and it is called, very originally, bound coagulase also referred to as clumping factor. The other one is freely excreted by the bacteria.

It makes a different which coagulase you are looking at. For the bound coagulase, you can use a slide test or a commercial or latex agglutination test to detect the presence of that coagulase where the free coagulase is detected by a tube test.

Now, let me explain what each of those tests are. The slide test--what that means is you take your organisms from that pellet or from a plate. You suspend it in a small drop of water and then you mix with that the plasma. If Staph aureus is present, the organisms will clump together and

it happens within about ten seconds.

Another version of this test is commercial latex-agglutination test where, on latex particles, they have immobilized the antibodies to the bound coagulase as well as antibodies to protein-A which is specific for Staph aureus. If the latex particles clump in the presence of the organism, then that is considered a definitive positive test for Staph aureus.

The slide test is positive in about 85 percent of the isolates of Staph aureus. That percent actually will fall if you don't have a heavy enough inoculum to be able to perform the test properly. The latex test has a very good sensitivity and specificity. It approaches 97 to 98 percent sensitive and specific.

There are some organisms that will give you a false positive slide test. I have listed them here on this slide. There are also some organisms that will give you a false positive tube test. The tube test is that you take a tube of about a half a milliliter of plasma. You suspend

your organism in that and you incubate it for four to 24 hours.

Almost all Staph aureus isolates will be positive within four hours with that test. Some, though, require extended incubation and you have to incubate them overnight before you can have a definitive negative test.

What all this means for the coagulase test is that, if the slide test is positive, in general, you consider that definitive for Staph aureus and you report that. If the slide test or latex test is negative, then you have to confirm that negative reaction with the tube test which would take four to 24 hours. Again, the protein-A is just a variation of the latex agglutination test.

(Slide.)

Genetic probes for Staph aureus; GenProbe has developed the probe they market as AccuProbe that is used to identify Staph aureus. It is a single-stranded DNA probe with a chemiluminescence label on it that is complementary to the ribosomal RNA in Staph aureus. The advantage of targeting

ribosomal RNA is there are about 10,000 copies of the RNA that is present so you have an inherent amplification of the test using this approach.

The test inoculum is recommendedly prepared from a subcultured plate or, again, from that pellet of the broth. It can be prepared from a broth culture. The recommendation by the manufacturer is the turbidity has to be a McFarland 1 standard which is very heavy inoculum for practical purposes, much heavier than what you would see when a blood culture is initially detected as positive.

The test time to perform this cell-lysis hybridization and detection is less than one hour. So this would truly be considered a rapid test. Marlow, last year, reported that the limit of detection with seeded blood cultures was approximately 10,000 colony-forming units per milliliter with this method. That is at least 10-fold to 100-fold more sensitive than the limit of detection for the blood culture instruments.

In other words, with a seeded study, it

appears that you could use the blood culture broths directly to do this test. I think additional tests have to be performed to confirm this but if this, in fact, is true, this would be an attractive alternative for identifying Staph aureus rapidly from a blood-culture broth.

Still, the way that you can get around the possible problems of sensitivity here would be to pellet the organisms in a concentrate and use that to perform the test. That should work very successfully.

(Slide.)

The last technique for identification of staphylococcus that I wanted to mention is fluorescent in situ hybridization or FISH test. Applied Biosystems, which used to be called Boston Probes, developed a FISH test using synthetic peptide nucleic-acid probes that target, again, the messenger RNA of the specific bacteria, in this case, Staph aureus.

They have a number of probes for different bacteria but the one that we are interested in

today is the one for Staph aureus. The peptide nucleic-acid probe is a synthetic pseudopeptide that hybridizes complementary nucleic-acid targets. Essentially, it is a synthetic peptide backbone with nucleic acids attached to it that would match up and be complementary to the nucleic-acid target.

The probes have the advantage of a higher specificity and more rapid hybridization kinetics compared with traditional DNA or RNA probes. In addition, the hybridization can be performed in a wide variation of salt concentrations which allows the speed in which this reaction can be performed.

The probes also have a fluorescent label on them which allows detection by fluorescent microscopy.

(Slide.)

I apologize for this picture. This wasn't really what I wanted to show you. What I wanted to show you is what is here in this lower right-hand corner but I am not sophisticated enough with computer to figure out how to cut that little picture out and show that alone.

So this is from one of Boston Probe's research articles that were published. It showed a series of different organisms. There was an E. coli. Salmonella is No. 2. No. 3 was Pseudomonas auruginosa and No. 4 was Staph aureus.

The first two columns going down showed auto-fluorescence. The next four columns, they used specific probes. So, under C, it was the specific probe that was for the E. coli and only the E. coli is fluorescing. The second one was for Salmonella. The third one was for Pseudomonas and the last one, in the lower corner here, was the specific probe for Staph aureus.

Truly, that is what it looks like when you perform these tests. They really do jump out at you. The organisms can auto-fluoresce and they have corrected with special filters for the auto-fluorescence. So it really is a fairly nice, in my experience, and we have used this now for about three months; it is a system that works fairly nicely.

The downside of this is the total test

time is approximately two-and-a-half hours. It is not a problem if your blood cultures are detected early in the day but if it is detected late in the day and, because of the, I think, relative sophistication of the interpretation of the reaction, it is not a test that can be performed off-hours. There have been three studies using these probes; specifically, the Staph aureus probe with positive blood-culture broths and the sensitivity and specificity for each of the studies was 100 percent. So it appears that this is a very sensitive and specific reaction when used with blood-culture broths.

I think that was my last slide.

DR. LEGGETT: Thank you, Dr. Murray.

Questions from Committee

DR. LEGGETT: Are there any questions? Don?

DR. PORETZ: Through the years, it is obvious that we are seeing more and more blood cultures being reported back as coagulase-negative Staph. Not all those patients have lines in place.

Do you think it is because of the way the blood is collected? Do you think it is because what is happening in the laboratory? Why are we seeing so much coagulase-negative Staph in blood cultures?

DR. MURRAY: I could probably make one comment about the laboratories. In my opinion, one of the advantages for the new blood-culture systems is they are noninvasive systems. Once you have inoculated the blood into those, you don't go back into those bottles where traditionally, either with manual systems or with the early automated systems, there are multiple entries into the bottles.So it is most likely the collection problems.

DR. PORETZ: I get the impression, after watching our laboratory technicians draw blood, at least in my hospital, they are not as careful as they were several--they are being--you know, it is a matter of dollars and cents. They speed these people up from person to person. I think that is probably the major reason and we are getting what we are paying for. We are, therefore, treating more patients than we need to treat, unfortunately.

DR. MURRAY: Very clearly, and there have been, I think, excellent studies that have looked at this, if you have a dedicated phlebotomy team that collects blood cultures, you get much better results. If you have technicians that have other responsibilities, if you have nurses that have other responsibilities, you have medical house staff that are doing a lot of different things, they are not trained well and they don't take the time to do it properly.

Again, my experience is if you look at where you have problems, you can usually identify key areas. That is really where the laboratories need to focus their attention in getting the proper cultures collected.

DR. LEGGETT: John?

DR. BRADLEY: It is wonderful to see the progress in molecular techniques in increasing how quickly we can identify organisms once they have come out of culture. However, at the bedside, for enrollment in a study, what we would really like is a test, a molecular test, we can do on plasma of

the sick patient so that, within two-and-a-half hours of entering the hospital, we would have something to let us know whether they are infected or not. Can you comment on progress in that direction?

DR. MURRAY: I think that the difficulty that, if you look from the microbiology perspective, the difficulty that you are working with is there are very small numbers of organisms present in the blood and that you have to amplify that. Not every company that makes molecular probes has targeted blood cultures as the place to go because, if you come up with a successful system, it is wonderful because there are a lot of people that would want to run those tests.

I am not optimistic about that, but possibly that will happen. Other approaches would be to look at a patient's response to the organisms, and so you look at cytokine profiles. There is a lot of work that is being done with that as well. And that is part of problem. It is not specific.

DR. LEGGETT: Barth?

DR. RELLER: I would like to add three more reasons, Don, why there are more positives. One is where the blood is collected from. There are more and more catheter draws because it is convenient. Two is time is money, and the speed. If one uses povidone iodine, as Pat pointed out, it takes time so that you have--and the Gram-positives are the hardest ones to kill or to disinfect.

The third thing that is, I think, unequivocal and has been shown in controlled clinical trials is the newer instruments including media for institutions that use charcoal and resin-containing bottles. They are more sensitive. But they are also more sensitive at picking up that solitary coagulase-negative staphylococcus that is derived from the first two issues.

So there is a tradeoff. You get more reals but you unequivocally get more contaminants. I would reinforce Pat's assessment of John's query about PCR. PCR, or nucleic amplification, is fantastic for some entities where the number of

targets is large; acute HIV infection, hepatitis C, HSV, et cetera. Pat emphasized it is unequivocally true, many, and shown by Washington, Murray, others, at least half, more than half, of real staphylococcal bacteremias were less than one organism per ml, so that one would have a large volume.

There are currently not yet processes in place, not that it couldn't be developed, that one could extract the 20 to 30 mls of blood, because if you don't have a target, you don't have a positive nucleic acid.

DR. LEGGETT: Dr. Murray, a question. On your slide about interpretation of culture results, it stated that Staph aureus is detected in less than 24 hours and other Staph greater than 24 hours. Are you implying less inoculum or slower growth?

DR. MURRAY: It probably is not the inoculum effect. It is probably more related to the rate of growth of the organisms. If you just look at colonies of Staph aureus and colonies of

coagulase-negative Staph on a plate, generally the Staph aureus is a much larger organism, the colonies. So it is growing faster.

The inoculum is an important issue though because the time to detection is influenced by the number of bacteria that are present. One way of assessing whether a catheter is the source of a positive culture, or a septic patient, is to look at how fast the organisms--how fast the cultures collected from a catheter group compared with cultures collected at the same time from a peripheral vein.

DR. LEGGETT: Any further questions? Thank you, Dr. Murray.

Do we want to take a fifteen-minute break now? I think so. I was chided by one of the speakers last time because I wasn't accounting for older bladders. So it is now 10:15. Let's come back at 10:30 for the Open Public Hearing.

(Break.)

Open Public Hearing--Extra Session

DR. LEGGETT: This will begin our extra

session of an Open Public Hearing which was not on the Federal Register Announcement.

Before we have Dr. Tally speak to us, I would like to make the following announcement. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement

to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Tally?

DR. TALLY: In the spirit of what Jim just said, I am the Chief Scientific Officer of Cubist and I am a stockholder of Cubist.

(Slide.)

I would like to thank the agency for inviting Cubist to present at this important advisory committee meeting. We are currently in trial in a study of Staphylococcus aureus bacteremia endocarditis. I would like to present some of the experience we have had with this particular study.

I will give you the summary up front using the old teacher attitude of I am going to tell you what I am going to tell you, tell you, and then review it at the end.

(Slide.)

Staphylococcus aureus bacteremia, as we have heard from the previous speakers, is a significant unmet medical need. It is a heterogenous population which includes endocarditis and in these heterogeneous populations, there are different outcomes. There is a lack of a placebo effect with Staphylococcus aureus bacteremia and I will address that during this talk.

It is a difficult study to do, a bacteremia endocarditis study, but it is possible and we will look at that today. However, when we look at this, traditional noninferiority assessment may not be best or the only association of efficacy in this seriously ill group of patients.

(Slide.)

What is the high unmet medical need? We have heard, from the earlier speakers, that Staph aureus is a leading cause of bacteremia. It is a virulent organism. Indeed, it is one of the premier pathogens to infect man. It was discouraged in the preantibiotic era. It leads to endocarditis, metastatic infections and/or death.

As we have heard this morning, Staphylococcus aureus bacteremia is both a cause and a result of endocarditis. Finally, there is changing epidemiology, as we have heard today and, in that changing epidemiology, it is a therapeutic challenge and that is compounded by the increasing resistance to beta-lactam drugs and the increasing tolerance to vancomycin.

(Slide.)

What is the mortality and what is the frequency of Staph aureus bacteremia? This is data just published in August from the SCOPE study looking at 20,000 isolates of nosocomial bacteremia published in CID. When you look at coag-negative Staph, it is 31 percent of the isolates, the coag-negative Staph, with a crude mortality of 21 percent.

With Staph aureus, incidence of the 1999 survey, SCOPE survey, was 16 percent in 2004. It has jumped to 20 percent of the isolates. So Staph aureus as a cause of nosocomial bacteremia is increasing. The intended mortality, the crude

mortality, with Staph aureus, in this particular study was 25 percent.

(Slide.)

What about the placebo effect. This is data that was mentioned earlier. The Skinner study published in the Archives of Internal Medicine in 1941 looked at the outcome in patients with Staph aureus bacteremia and the case-fatality ratio was 82 percent. You will notice if you are 50 or older, which most of us are in the room, the mortality goes up to almost 100 percent.

With this, when you look at Staph aureus endocarditis non-treated, it is 100 percent fatal as are other endocarditises in the preantibiotic era. So the placebo effect in Staph aureus bacteremia or endocarditis is little or none.

(Slide.)

The next confounder in Staph aureus bacteremia is whether the patient has a MSSA bacteremia or an MRSA bacteremia. This is a slide from Sarah Cosgrove's meta-analysis looking at that. If you look at mortality with MSSA, it is

23.4 percent. With MRSA it is 36.4 percent. She controlled for confounding variables in clinical backgrounds. So there is a consistent finding that mortality is increased when you have MRSA causing the infection.

(Slide.)

When you do have MRSA, the main therapeutic modality has been vancomycin. The problem emerging from vancomycin has been the emerging resistance. We saw VRE outbreaks in Europe in '86. It continues to today. VISA was first reported from Japan in 1996. We still see it albeit it is very low. Heteroresistance in vanco was noticed by the CDC in 2001 and it continues to be a rising problem.

More recently, we have had vancomycin-resistant Staphylococcus aureus albeit there are only three isolates known at this time.

(Slide.)

When you do look at vancomycin in this particular area of therapy for MSSA and MRSA, two things come out. One, Chang, in an analysis of

over 500 cases of bacteremia, looked at MSSA, whether it was treated with vancomycin or nafcillin. In that study the conclusion was that nafcillin was superior to vanco in the treatment of MSSA bacteremia and why most people recommend switching off vanco to nafcillin when you have nafcillin-susceptible.

More recently, there has been disturbing data with these heteroresistent strains and vancomycin has been known to fail in MRSA bacteremia back into the early 90s in studies coming from San Francisco.

The heteroresistance and tolerance problem probably is the most common problem we are seeing now and it has increased and heteroresistance is noted to be associated with increased failures.

The most recent paper in JCM in June of this year looked at a biased sample of failure patients, looking specifically at the MIC of the organisms to vanco, came up with a surprising result. By NCCL criteria, an isolate with an MIC or 4 or less to vancomycin is considered

susceptible. However, when the group at the Deaconess looked at 30 isolates, it had some rather disturbing outcome when you broke up the isolates based upon the MIC.

Those isolates with an MIC of 0.5 or less, there was a successful outcome in this group of 55 percent. The overall group of 30 patients, it was a 23 percent favorable outcome. However, if the isolate had an MIC of 1 to 2, the favorable outcome was 9.5 percent and that is approaching what we saw with the placebo effect that Keefer published in 1941.

So one has to look at vancomycin in this group of patients and particularly wonder about these ones with MICs of 1 to 2.

(Slide.)

So, with that background, when we were looking at our drug, daptomycin, and how to guide physicians in treating, and, particularly, what we were asked is how do we treat bacteremia, we made the decision back in 1999 to look at patients with bacteremia and endocarditis because, at that time,

endocarditis is a registerable indication according to FDA guidelines.

In consultation with the FDA, we undertook at study of daptomycin and infective endocarditis and bacteremia to specifically Staph aureus. The criteria to get into the study is you had to have a positive blood culture for Staph aureus. It is multicenter, both in the U.S. and Western Europe. It was randomized. But, because of safety concerns, it was an open-label study which adds complexity that I will talk about in a minute.

We did add a blinded external adjudication committee. It is a comparative control and it was nafcillin versus vancomycin. In the beginning, we just treated bacteremia and right-sided endocarditis. There was an amendment of the protocol in April of 2004 to include a left-sided endocarditis.

(Slide.)

What were the challenges in this study? You have heard this morning that Staphylococcus aureus bacteremia is a heterogeneous group of

patients. We use the modified Duke criteria to try and give some semblance of what type of patient we had at admission criteria. This is the phenomenon. The clinician is confronted with a positive Staph aureus blood culture and you don't know which group they are going to fall into. You only determine that during the course of therapy with many diagnostic tests.

What we did is we classified our patients by the Duke criteria into definite or possible or not infective endocarditis. Part of that was a centralized reading of our echos, not leaving it to the original site. Finally, at the end, there will be an overall determination of responses in each subgroup; that is left-sided endocarditis, right-sided endocarditis and bacteremia.

This is a difficult study to enroll and I will show you the magnitude in the next couple of slides.

(Slide.)

So what we did is enrolled numerous sites. There were some ethical considerations and that was

you are treating patients with a high mortality if they have endocarditis. So the treating physician has to know. We looked at that open-label design. We also put in place a safety data-monitoring committee to make sure there was not a safety issue in the ongoing study.

What about the bias due to an open-label design? We addressed that somewhat with the blinded independent external adjudication committee. It is composed of ID experts that are experts in infective endocarditis. They will determine diagnosis and outcome.

Finally, with the type of study here, we have heard about relapse, you need long-term follow ups. So the test of cure is actually out at six weeks and a post-study visit is actually out three months. So the length of the study is rather long.

There are extensive inclusion and exclusion criteria which affect the conduct of the study and it is related to the drugs used and the patients being enrolled.

(Slide.)

How did we make out in this study? When we looked at our diagnosis, and we are over 200 patients which is what are target was, and we looked at, by the Duke criteria, at these patients, about a third of them did not have IE based upon the Duke criteria and would consider those having bacteremia.

We had a large group that were possible IE. They met the Duke criteria but they did not have a positive echo. Finally, we also had a smaller group that had definite infective endocarditis. It is proven by echocardiography.

(Slide.)

How many patients did we have to screen to get this over 200 patients? We screened over 5,000 patients to get this over a two-and-a-half-year period. But it is doable. And we are, at this point--right now, we are in discussions with the FDA on going forward with this particular study.

(Slide.)

So I am back to the summary from the beginning. There is a significant unmet medical

need. I think it has been brought out time and again this morning. The heterogeneous population includes patients with endocarditis and these heterogeneous populations all have different outcomes. So you are going to have to do some type of subanalysis of those groups.

There is a lack of a placebo effect in this so it raises some questions we will get to. It is a difficult study to do, expensive, but it is possible to do these studies as we have shown.

Finally, traditional noninferiority assessment may not be best in this serious illness or the only assessment of efficacy and I would throw that open for discussion at the end.

Thank you.

DR. LEGGETT: Thank you, Frank. We will take some questions. Alan?

DR. CROSS: When you said that you screened over 5,000 patients, was that 5,000 patients with positive blood cultures or with Gram-positive positive blood cultures?

DR. TALLY: It was 5,000 patients with

positive blood cultures.

DR. LEGGETT: Jan?

DR. PATTERSON: I was wondering on that Sakoulas JCM 2004 study, the vancomycin--we know that physicians tend to underdose vancomycin. I was wondering, did they use a 10 milligram per kilogram dose and/or were there any trough levels measured?

DR. TALLY: There were trough levels and they were, I think, above 15. So they took that into consideration with these.

DR. LEGGETT: Frank, could you elaborate a little bit about the exclusion--was it mostly the inclusion-exclusion criteria that you had the 5,000 but only 200 enrolled?

DR. TALLY: I have my Dave Letterman list of ten reasons. The biggest reason, in our study, turns out to be creatinine clearances below 30. Our drug is cleared by the kidney. We didn't have guidance in that area so it was a major exclusion criteria in this. And, indeed, that is something we are working on now to try and include patients

in the future with ongoing studies of patients with renal failure being evaluated with a specific dosing regime.

It was not the only reason. That was a primary reason and, in those patients, they probably had other reasons for being excluded also. But, also, there were a whole bunch of other reasons. One, they were already on the drug for greater than 48 hours, it was effective. Two, you couldn't get the consent in this serious illness. Three, there was renal failure. Four, they were in imminent threat of death so we didn't want to put morbid patients in. Fourth--let me pull out my sheet, my cheat-sheet for that.

A large group where they intravascular material that couldn't be removed were excluded. Severe neutropenia. Elevated bilirubins above 3. So there were a number of these criteria to try and focus on the disease and get it. We are not giving out the exact numbers on that. We have submitted all of that data to the FDA. We will be discussing that and it will come out sometime when we complete

the study.

DR. LEGGETT: Tom?

DR. FLEMING: Could you clarify your last point? It is somewhat vague. You haven't gone into any details about what type of noninferiority assessment was planned.

DR. TALLY: Excuse me?

DR. FLEMING: Could you clarify your last point about the noninferiority assessment.

DR. TALLY: Not being a statistician, I can't. I don't know what type of analysis should be done and that would be something we should talk about. But I think with the number of patients that you have to enroll, you would have to screen, to enroll just 200 patients. And then you have to do a subset. If you want to look at the subset analysis of the different groups of patients within here. It is going to make it an impossible study to do if we are doing a noninferiority study.

So one would like to know if there are alternate ways to study this group of patients that, one, do not have a placebo effect; two, have

a definite endpoint of you either clear the bacteremia or you don't. Third, to take into those the effect of not being able to do a study to assess all of these subgroups.

So I, personally, don't know what type of analysis should be done and would throw that out.

DR. FLEMING: Just to lay out the principles here, though, the analysis that you would do should allow you to conclude that you have an efficacious intervention.

DR. TALLY: Correct.

DR. FLEMING: And in a setting that you are referring to here as--you are calling it lack of a placebo effect. I think what you are saying is a setting where you are going to have very few favorable outcomes in the absence of effective therapy.

DR. TALLY: Correct.

DR. FLEMING: But where there are effective therapies then a critical question is to ensure that an intervention isn't clinically meaningfully worse than what, in fact, you could

achieve with existing therapies which also is, in fact, addressable through a noninferiority paradigm.

DR. TALLY: I think you hit on it. It is the clinical evaluation of it and that is what we are in discussion with the FDA right now.

DR. FLEMING: Celia?

DR. MAXWELL: On your Slide 12, on the diagnosis of enrolled patients by the modified Duke criteria at baseline, I had a question--two questions, actually, of the definitive and the possible infective endocarditis, what was that in actual numbers and also, of these two populations, were any or what percentage of them in each of these categories were shown to have vegetations, let's say, on echo.

DR. TALLY: The definites had echo evidence of vegetation.

DR. MAXWELL: All of them. And what number was that?

DR. TALLY: Oh; we are not giving out the numbers at this point in time.

DR. MAXWELL: Okay.

DR. TALLY: Because the numbers are not complete. We are on an ongoing study where there are a number of patients where we haven't determined--they are under analysis. So I am constrained from giving out numbers because, in addition to being regulated by the FDA, I am also regulated by the SEC. And I don't want to give out any misleading information.

DR. LEGGETT: Don?

DR. PORETZ: Frank, do you anticipate, if this drug is of value and is approved, is one going to be, when they are treating infective endocarditis, obligated to get serum levels of the drug?

DR. TALLY: Since I haven't seen the data and the study is still ongoing, I think we have to wait to draw that conclusion. We had built into the study a pharmacokinetic study on all patients that we will be able to use when we look at the outcomes when the study is closed down and the blind is broken.

DR. LEGGETT: Barth?

DR. RELLER: I just wanted to comment that, at first, it seems the 200 out of 5,000 is a small number. But it is exactly what one would expect given the physiologic exclusions. I base that on the largest review published in the '90's on bacteremia; exactly 9 percent of all positive blood cultures grew Staph aureus assessed by an infectious-disease clinician to be true, which were almost all of the Staph aureus.

What it is telling you is that half of all blood cultures obtained in tertiary-care hospitals in the United States are contaminants or unknown. So you do the numbers and, if you took 1,000 reals relative the positive, same institution, it is 9 percent. So basically it is capturing half of the ones who really have it.

DR. LEGGETT: Yes.

DR. FETZER: (Inaudible comments.)

DR. LEGGETT: Could I ask you to speak into the microphone, please, and identify yourself.

DR. FETZER: Olaf Fetzer, senior vice

president, Cubist Pharmaceuticals, responsible for R&D. I just wanted to mention to Frank, as a correction; of the 5,000 screened, these were all Staph aureus confirmed.

DR. RELLER: It wouldn't make it much different if it were all staphylococci in coming down to--but then there are other reasons why people chose not to enter someone into the trial apart from the exclusion criteria mentioned.

DR. TALLY: In response to Bob's question, one, and to clarify, the only patients that were screened has positive Staph aureus cultures. So that has been eliminated right away. There are a whole list--there are about 30 reasons why patients didn't get into the study. I gave you some of the top ones and I don't have the full list right with me.

If somebody drops out for one of the higher reasons, it doesn't mean they have a lower reason for exclusion. What it is saying is that this--and it is a very sick patient population--when you build in your exclusion and

inclusion criteria, it eliminates a lot of patients. It is just getting that proper window where they haven't had other therapies and getting a patient to consent to your study and to get the physician to take out devices is problematic in this group of patients.

DR. RELLER: I was just running the numbers based on the earlier question and on the comment that it was all positive cultures, not all cultures obtained. If one did all positive cultures, you could count on, at most, 9 percent.

DR. LEGGETT: Thank you. Let's move on. Thank you, Frank.

Our next speaker is Dr. Powers who is going to talk to us about clinical-trials issues with studies of Staphylococcus aureus bacteremia which will be followed, again, by questions from the committee.

Clinical Trials Issues with Studies of Staph aureus Bacteremia

DR. POWERS: Thanks, Dr. Leggett.

(Slide.)

I think that is a good introduction because what Dr. Tally brought up--

DR. LEGGETT: Excuse me, John. I have to close the Open Session.

DR. POWERS: Oh; go ahead.

DR. LEGGETT: The open session is closed.

DR. POWERS: That took care of that. What Dr. Tally brought up was that it was very hard to evaluate the endocarditis subset within the group of people with Staph aureus bacteremia. But what they did find was 5,000 people with Staph aureus bacteremia.

So what I would like to talk about today is can we define a new indication of primary bacteremia due to Staphylococcus aureus and then maybe look at subsets within that to try to evaluate those patients.

(Slide.)

So the first thing we are going to talk about is actually defining this indication and ask the committee whether they think that this is a worthwhile indication for people to pursue and does

it actually add some information for clinicians.

Then we would talk about the place of this potential indication in a clinical-development program and what kinds of preclinical and prior clinical-trials work would be helpful in evaluating a drug that would be potentially helpful in this disease and then, finally, go through some of the issues in designing and analyzing clinical trials of this potential indication.

We will go through some of those issues of selecting the appropriate patient population to study, talk about how would we evaluate endpoints with what Dr. Nambiar brought up about how would one evaluate metastatic disease that may occur on treatment, talk about this issue of selection of duration of therapy, the issue with controlled drugs--and we will go into a little bit about this dictum of vancomycin and nafcillin and how they compare to each other, and then some of the statistical considerations including the question Dr. Fleming asked about noninferiority.

(Slide.)

So the first question we would like the committee to ask here, and I am going to do this talk in terms of questions and then put some of the pertinent information underneath it. So, should primary bacteremia due to Staph aureus constitute a separate indication?

Before we answer that, we actually have to say what is an indication. Well, an indication and the patients actually studied should be something that we can clearly define. That is for two reasons. One, obviously, we need to be giving some information to clinicians about how they appropriately select patients for treatment with that drug once it is determined to be safe and effective. Also, we need to be able to write that into prescription product labeling so that people can understand who was studied and where the drugs should be used.

So what we are suggesting is that maybe one definition of primary bacteremia due to Staph aureus, and this gets back to what Dr. Patterson asked, we are not defining in the same way as it

was defined in some previous trials. What we saw was that it is variously defined depending upon how you look at it.

So our suggestion here would be that it is evidence of systemic signs and symptoms with positive blood cultures for Staph aureus and no other identified source of infection at the time of enrollment. The reason why we brought up signs and symptoms is something that Dr. Reller just brought up, that maybe as much as 50 percent of positive blood cultures don't represent real disease.

What the committee had discussed in the past, in 1998 and 1999, was that bacteremia alone is not an illness. We need to link that to some signs and symptoms that the patient actually has.

It shouldn't be that hard because, usually, clinicians draw a blood culture when the person is having some systemic signs and symptoms. So then the question comes up is should one differentiate from secondary bacteremias--that is, patients who have a known source of infection such as pneumonia, complicated skin infections, et

cetera.

What the committee had told us back in 1999 was they were concerned that there may be differential efficacy of drugs based on the site of infection. We have certainly seen recent drugs that were effective in, say, complicated skin but did not look effective in other body sites like pneumonia. So, depending upon where the patient's original site of infection is may be important in determining drug efficacy.

Also, bacteremia related to an intravascular catheter--when we looked through a lot of this literature--is often really a diagnosis of exclusion. Sometimes it is based on a positive catheter tip but, again, when we went back to the 1970s and tried to evaluate where does that information come from on positive catheter tips, again, there really is no gold standard to say what were those things compared to to determine that a positive catheter tip actually implied that the person had a true catheter-related infection.

So the question came up, since it is often

a diagnosis of exclusion and what we have heard from people in industry that we will go over this afternoon is that it is very often difficult to get that piece of information from the catheter because it has often been discarded by the time you get around to the patient.

So could we devise an indication where intravascular-catheter-related infections were subsumed under this primary bacteremia indication. But, really, the question is would this indication provide useful information to clinicians. If we already know that a drug is effective in Staphylococcus aureus infections with a primary source of infection, would this provide this some additional data to knowing that the drug is effective in pneumonia, complicated skin, et cetera.

That brings up something Dr. Tally just talked about. Would this indication provide us the opportunity to study patients that would not be included in those with a primary source of infection. Namely patients with endocarditis would

be the big issue there.

(Slide.)

In fact, it is such an important issue that does efficacy in primary bacteremia due to Staph aureus imply that the drug is effective in endocarditis. Clinically, what we always worry about when you see a person with a Staph aureus in their bloodstream, especially if they don't have an identified initial focus of infection, is they may have an occult case of endocarditis.

So why is that important in terms of a clinical trial as well as clinically? Because, first of all, it implies different outcomes in the patient and, in fact, Dr. Tally referred to a paper by Chang in Medicine. There is another paper by the same authors in that same journal that looked at risk factors for outcome in people with Staph aureus bacteremia, 31 percent mortality in the people who had endocarditis versus 20 percent in the people who didn't. So big difference in outcome if you have endocarditis or not.

It also may imply a different duration of

therapy as well, and that remains controversial; two weeks, four weeks, six weeks, what would be the appropriate duration in these people.

So then the question comes up is can these drugs be studied without examining efficacy in endocarditis and, even within endocarditis, are there differences between right- and left-sided disease. So one of the things we would like to ask the committee is can these drugs be studied in a staged approach of first studying uncomplicated Staph aureus bacteremia or at least people unlikely to have a complication; then study right-sided endocarditis; then study left-sided disease.

In addition, how would we approach drugs that may not demonstrate some potential efficacy for endocarditis based on either in vitro or animal testing but still may be effective in patients who have a primary source without endocarditis.

(Slide.)

So the next question that comes up is where would these kinds of studies fit in the overall clinical-development plan for a new drug.

We brought these issues up in April of 2004 at a public workshop co-sponsored by FDA, the Infectious Disease Society of America and the International Society for Antimicrobial Pharmacologists.

Some of the participants, when we brought this up, a little to our surprise, were very hesitant about going forward with studying drugs without some prior information that the drug may be effective given the serious nature of this disease and the potential for development of endocarditis.

(Slide.)

One of the things that the folks at that meeting suggested was that there should be some data from trials in this indication and that this kind of indication probably would not be the sole basis for approval. In other words, if a new drug came forward and this is the only thing they wanted to study, that that might be problematic and that we would probably look at this in terms of the overall efficacy of a drug in treating serious Staph aureus infections.

So, again, they expressed this view of

that we needed some more infection. So then the obvious question is what kinds of information would be helpful prior to studying a drug in a serious disease like this.

(Slide.)

The first question is what kinds of preclinical studies would be helpful in forming these hypotheses about potential efficacy and safety in this indication. And that would include both in vitro data and animal models. The in vitro data would consist of looking at the biological activity against isolates of Staph aureus and that brings up another interesting question about what is the clinical significance of bacteriostatic versus bactericidal drug.

Dr. Pankey and colleagues wrote a very interesting review of this just recently in March 2004 in Clinical Infectious Diseases where they actually proposed the hypothesis that no drug is really all bactericidal or all bacteriostatic, that the way in which we define these things is really 80 percent or so killing with a bacteriostatic and

99 percent of so with bactericidal and that, by altering the conditions of inoculum, pH, et cetera, that you can actually alter whether a drug is bacteriostatic or bactericidal in the test tube.

The real question, though, is what is the clinical significance of bactericidal versus bacteriostatic. We have all been taught that, in serious diseases where the antibiotic may not penetrate or there is little help from the host immune system such as meningitis and endocarditis, that at least, in animal models, it appears that bactericidal drugs look more effective in those models.

So the question is what do you do, then, with a drug that appears bacteriostatic in the test tube. Would that be something that folks would be able to study in this indication or could we use that staged approach that we talked about earlier.

Again, could we look at, then, some animal models of infection to give us a better idea of how these drugs may work given that in vitro may not reflect clinical outcomes perfectly and what kind

of animal models would we need. Endocarditis would seem to be an obvious one but are there other potential metastatic sites of infection like bone that we would want to look at animal models as well.

(Slide.)

Then what clinical experience would be helpful in evaluating a new drug for this indication? We know that spontaneous generation in the bloodstream was done away with a number of years ago as a potential reason why people have organisms so, obviously, these people have a primary site. It is just that we don't find it. So patients with no primary site, it is still coming from somewhere although it may be occult.

The serious nature of this illness and, again, those potential differences in efficacy of drugs based on the primary site of infection, again, would weigh against this being the sole basis of approval for a new drug.

So one of the things we would like the committee to address is what kinds of data from

clinical trials of infections of sufficient severity where Staph aureus would be a potential pathogen would be helpful in evaluating in new drugs for this indication.

Some of the ones we thought of were hospital-acquired pneumonia, community-acquired pneumonia sometimes especially after influenza outbreaks can occur due to Staph aureus, complicated skin and skin-structure infections and are there some others that the committee might suggest where Staph aureus is a common pathogen that we may be able to look at.

So I would like to go into now a bit of--now that we have gone into the natural history of the disease, how will we actually design and analyze clinical trials for this indication. One of the reasons we did the talks the way we did today was it is very important to look at the natural history of a disease and to design trials based upon that natural history.

These clinical trials obviously need to provide information that is useful in clinical

practice but it is a very important distinction to realize that clinical trials are not clinical practice. We do lots of procedures to people in a clinical trial that are not routinely done in clinical practice but, perhaps, the biggest difference is that, in clinical practice, we give a drug and we don't care why the patient gets better as long as they recover.

However, in a clinical trial, what we are trying to do is to ascribe causality of results to the drug that was administered, a very different thing than what we do in clinical practice. So, to allow us to do that, we use the scientific method and that is we hold as many factors constant as possible other than the drugs administered to the patients so that we can ascribe the causality of those results to those drugs that were administered.

The Code of Federal Regulations actually says this in a very nice way. It says; the purpose of performing any clinical investigation is to distinguish the effects of the drug from other

influences such as spontaneous change in the course of the disease, placebo effect or biased observations. There are a number of other things such as potential confounders that may come into the trial like concomitant medications, et cetera, that also impact on that as well.

(Slide.)

So I wanted to sort of show this as a map and talk about the places where potential bias may creep into a trial and then try to address some of these in terms of primary bacteremia due to Staph aureus indication.

So what we first do is we obviously take a group of people as a whole who have the disease or even, more importantly, that we think might have the disease and then try to define the patients who would enter into the trial. Clearly, the first step there is we want to make sure they have the illness that we are trying to study.

The issue here, too, is that this population needs to be heterogeneous enough to extrapolate to the people we are going to treat in

practice but homogeneous enough to be able to make some conclusions about drug efficacy. Then we randomize people and, hopefully, blind this as well, talk about things that may occur while patients are on therapy, appropriate endpoints and how we analyze the data.

(Slide.)

So the first issue there is defining the patients who would actually come into the trial which is based upon the inclusion and exclusion criteria. Again, as I said, we need to strike a balance between a homogeneous enough population to study so that outcomes are not related to the differences in the natural history of the disease just like the Code of Federal Regulations said we are not trying to measure and that they are related to drug effects, but has to be heterogenous enough to be able to extrapolate this to clinical practices.

One of the first issues is we would need to differentiate among patients with Gram-positive cocci in the blood. Dr. Murray gave us a good talk

this morning about how we may be able to do this.

One of the issues we have seen is that if you go to the microbiology laboratory and try to use that as the way to screen for patients in these trials, what is going to happen is, a, you are going to get a lot of Staph epidermidis and, even if they have Staph aureus, those people are likely to have received some amount of therapy by the time you get back to the patient who is up on the floor.

So the question we like to ask the committee here is are there better ways of screening for patients than just getting the breakdown of who comes out of the microbiology lab. More and more, as we see these trials, we are beginning to see that especially in shorter-term illnesses that that one or two days of antibiotic that people get up front may have a big influence on the outcome at the other end. So that may not be an insignificant problem.

Again, these newer diagnostic tests that Dr. Murray talked about may allow us to differentiate Staph epidermidis from Staph aureus

prior to enrollment which would be a huge benefit because, otherwise, the drop-out rate from these trials may be considerable.

(Slide.)

Again, we know that there are different natural histories for various populations of patients in whom subsequent testing after randomization may show a source or a metastatic site of infection, such as endocarditis. Again, I mentioned the difference success rates and the different durations of therapy that may be necessary depending upon what infection site the patient ultimately has although it may be difficult prior to enrollment to differentiate those people.

As Dr. Nambiar presented, even patients with what may be considered uncomplicated disease such as catheter-related infections may subsequently develop metastatic disease. So all of these things we are looking at are risk factors for metastatic illness but does not obviate that the patient may then develop those sites of infection on therapy.

(Slide.)

One of the things that we always find very important at the FDA is what you call something and the name of an indication. So I wanted to be clear about some of the definitions that we are using here today. One of them was complicated versus uncomplicated disease. Again, looking through the literature, we found various definitions of what you would call this. In fact, in the study by Small and Chambers that Dr. Tally referred to, what we found is that what they called complicated was just somebody that continued to have fever which is a very different issue than what we saw as complicated in some other trials.

So what we put out as a trial definition for you folks to discuss is complicated disease would be patients who develop further clinical manifestations that were not present at the time of initial diagnosis that may portend a worse prognosis and/or need for prolonged therapy.

As Dr. Nambiar said, these can be divided into two categories; severe sepsis, ARDS and DIC

which usually occur within 48 hours but then that issue of metastatic sites of infection which may occur early on, may occur later, and some preliminary evidence that we found says may actually decrease with the institution of effective therapy. But you saw the limitations of the data that we were able to find.

What we haven't really found to be very useful is this distinction between community-acquired versus nosocomially-acquired infections. When we look through the literature, what we saw is this really wasn't referring to the geography of where you got the infection. It was really trying to refer to different host populations.

Although we have defined community-acquired versus nosocomial with diseases like pneumonia, the question is does it really help us here. When we went back and analyzed our data from the Focus Technologies database, we saw that these PVL-containing community-acquired MRSAs which usually remain susceptible to clindamycin,

tetracycline and trimethoprim sulfa were really mixed in with the multi-drug-resistant Staph aureus that you would normally think of as nosocomial when we evaluated only outpatient isolates of Staph aureus.

So what that tells us is sicker people are going home, getting mixed up out there in the community with the people who have community-acquired MRSA and so, when somebody gets sick in the outpatient setting, which one of those do they have. It is not really the fact that they got it as an outpatient that determines what is happening. It is really the host factors that determine it.

So our looking at this says this may not be as useful a distinction in clinical trials for labeling given that there is such overlap in the populations. If we tell a clinician, use this for community-acquired and that is a dialysis patient who is in and out of the hospital every day, that becomes very confusing to the clinician.

(Slide.)

So one of the issues here, obviously, is it is very difficult to stratify these patients at the time of enrollment. We brought up this morning this issue of could you wait a little while, see what happens to these patients and then treat them later. Well, that data that shows that DIC, ARDS and severe complications can occur within 48 hours would really argue against waiting for any period of time.

But, since we can't wait, these metastatic complications may occur after enrollment. So, how well do these risk factors that have been cited in the literature select patients who have complicated disease and uncomplicated and, therefore, with uncomplicated, could these people receive what has been called short-course therapy.

Nathan Fieldman and I did our fellowship at Virginia. One of our co-fellows, John Jernigan, did a study while we were there, or a meta-analysis, looking back at all the studies that have been in the literature up to that point in time on evaluating short-course therapy for Staph

aureus bacteremia.

What John and Barry Farr found was that many of these studies differentiating complicated from uncomplicated infection were retrospective and 10 of the 11 trials that they looked at that time were uncontrolled. It is very difficult to be able to make any real good assumptions about whether short-course versus long-course has any differences associated with it.

We, then, went back and tried to pull all the studies from 1993 to the present to see if there were any differences and all we found, again, was either observational studies or retrospective studies. So, again, even since 1993, there is not much new information that would allow us to be able to draw any firm conclusions about short-course therapy in this disease even if you had uncomplicated disease.

So one of the questions we are going to ask the committee today is how do we deal with that in terms of setting the duration of therapy.

(Slide.)

How useful are these risk factors that have been enumerated in the literature in the past in the clinical-trials setting. Well, these may be useful in clinical practice but some of these risk factors, like duration of fever and duration of bacteremia actually occur after the patient has been randomized.

The other thing is these are all based upon the fact the you have a known effective drug. So, if a person is on nafcillin and remains bacteremic for three or four days, you could say, well, I think that person has endocarditis but I feel comfortable leaving them on nafcillin. This is a different situation where we are now testing an experimental drug in this setting, so does duration of fever and of bacteremia say something about how well the drug is working.

So how could we then use an outcome to define who the patients are at the beginning of the trial. It seems like very circular reasoning.

(Slide.)

The other issue I wanted to bring up is,

since these risk factors are based on outcomes with known effective therapy--I brought that up already about experimental drugs--how should patients who develop a site of infection after randomization be handled. I think Dr. Fleming asked this question earlier. Could patients with no signs or symptoms at the primary site be left in the trial when they develop a site of infection on therapy and does that have something to do with the timing of when they develop that site of infection.

So, if a person ends up in the trial and, within three or four days, develop pneumonia, can we assume that that pneumonia was there? If they develop pulmonary emboli, does that mean it was there at the time? Even if it was there at the time, should we still call those people failures of therapy in order to actually analyze people evenly between the arms of the trial.

In the past, we have evaluated--in empiric febrile neutropenia trials, we have set a breakpoint of calling people baseline versus breakthrough infections. But that presents another

conundrum. If you set that breakpoint, suppose somebody gets the infection one day before versus the person who gets an infection one day after that breakpoint. Are those people really different. That is a real conundrum we are going to ask you to comment on today.

What is really important here, though, is patients would need some kind of standardized evaluation at the time of enrollment so that there are no potential differences between arms of the study in determining who has baseline infections and who does not.

So, if one study center decides, we are only going to do chest X-rays and another study center says, we are going to do chest X-rays, bone scans and CAT-scan everybody from head to toe, the total body "groapgram," then how would we match those two up. So there would need to be some standardized way. We realize you have to be practical about what you can do here and that we can't ask for every test in every person.

But, as Dr. Nambiar pointed out this

morning, that one study actually showed that you find what you look for. The harder you look, the more likely you are to find the primary site of infection.

So we are going to ask you today what tests would be appropriate and, given this issue that endocarditis is such a concern, would every patient need some kind of echocardiography to evaluate those patients for endocarditis given that even patients with catheter-related bacteremias may go on to develop subsequent endocarditis.

(Slide.)

So, again, should patients who develop a site of infection be considered clinical failures on therapy? Should one differentiate baseline from breakthrough infections? And, again, can that be part of what we consider as part of the endpoints in this disease.

When we actually evaluated this, and I will go back to the paper that Dr. Tally brought up by Small and Chambers that was published in Antimicrobial Agents and Chemotherapy in 1990.

What they did was they took patients and, if their blood cultures were negative, and yet they remained persistently febrile, they called those people failures.

If they had some other complication, even in the face of a negative blood culture, they were called failures. It is interesting that we use that data to say vancomycin may not be so effective. But now, when we are talking about clinical trials on the other end, how are we going to handle that and call those people.

So it seems, when we were discussing this, that a negative blood culture doesn't always tell you that the person is not going to go on to have some clinical complication down the line. So would a proper endpoint include not only negative cultures, which we clearly think are important, but also some other evaluation of how the patient is actually doing down the line.

The other issue is this idea of time to negative blood cultures. This has been commented on several times in the literature and probably

goes back originally to the Kourzanowski paper in the Annals of Internal Medicine in 1982 wherein patients with right-sided endocarditis, they tested nafcillin plus gentamicin versus nafcillin alone.

I put this in my category of urban legends of infectious diseases because we are always told that we should use gentamicin up front for the first five days. The first issue is that is now how the study was done because the patients got gentamicin plus nafcillin all along during the therapy and what they showed was that, in a subgroup analysis of only non-addicts, eliminating all the addicts, which consists of 11 patients on nafcillin and 19 on the combination, they showed 3.4 days of bacteremia in nafcillin and 2.9 days in nafcillin plus gentamicin.

A, is that a real difference anyway that is clinically significant, about a half a day's worth of difference and then, after that trial was done, people say, well there was more toxicity in the gentamicin arm, obviously renal insufficiency. They said, well, since it causes renal

insufficiency, let's just give the gentamicin for five days up front.

And that is what we recommend. And that is actually recommended in the American Heart Association guidelines. But that is not how it was studied. So that becomes an issue, too, for selecting control regimens which we will get to down the line.

But the real point here, in terms of this problem here, is that time to negative cultures didn't correlate with either morbidity or morality in that Kourzanowski study. So, even if you can make the blood cultures turn negative faster, what does it mean clinically for the patient down the line.

(Slide.)

The next issue is how should the duration of therapies in studies of this indication be determined. The first question is why is that even important to discuss. Again, the problem here is we leave this up to investigator discretion, we may introduce a potential bias that similar groups of

patients may be being treated with two weeks worth of treatment at one center and four weeks worth of treatment in the other and how would we compare those.

So this is a big issue because we know that there is significant variation in clinical practice even for uncomplicated disease. I know every time we brought this up when I was a fellow and we would have a Monday conference about this, the attendings would be throwing stones at each other back and forth about whether everybody should get four weeks regardless just because they have Staph aureus in their blood versus others who thought that you could select a population that should get shorter-course therapy.

In the terms of clinical trial, this would really need to be specified up front as to what duration of therapy would be appropriate for what patients.

(Slide.)

So the next question is how would appropriate control regimens be designed for this

indication. Let me go back, since I didn't hear this until Dr. Tally presented his, I want to talk a little bit about this vancomycin versus nafcillin distinction.

When we went back and actually looked through this data, there are no randomized controlled trials that actually compare those. The first study or the most recent one is the one by Chang which was published in Medicine in 2003. The problem there is that we need to really understand the limitations of some of this data.

While that study evaluated 505 patients in a prospective manner, it was an observational trial. An observational trial is not randomized and the problem with that is that it may not, then, account for some of the differences between the patient populations. Since it is also observation, they have no influence on how the patients actually are treated which means that things like management of the catheter is not controlled for in that population.

So what they did, then, was come up with a

relative risk for vancomycin. It doesn't mean that vancomycin is inferior because there is no direct comparison between vancomycin and nafcillin within that trial. So, again, there are some limitations in looking at that.

The study by Small and Chambers published in 1990 in Antimicrobial Agents and Chemotherapy evaluated all of 13 patients who received vancomycin and they were I.V.-drug abusers. Five of those 13 patients were considered failures. And, again, we know that 100 percent of patients are not cured when they have endocarditis. So what you really need is some control, which that trial did not have.

What they then did was they went back and they pulled several papers which had essentially between 10 and 25 patients, pooled them all together and tried to get an effect estimate for nafcillin. That, essentially, is an historically controlled trial. Again, the people that they called failures, I will just give you two examples.

One of their patients, the only

complication was fever. The patient was doing fine, was put on oral cefradine and was sent home and lost-to-follow-up. So that patient was called a failure. The question is you could legitimately ask, well, did that patient have fever because of drug fever or because the person actually wasn't getting better from their endocarditis. With the lost-to-follow-up, it is hard to tell.

The other patient received nafcillin and tobramycin for four days, then got vancomycin for 12 days, then was switched to cefazonlin and then has a surgery down the line even though there were organisms found in the valve at the time of surgery. The question is, again, is that a failure and which drug failed? That person got four different regimens along the way and yet that was considered a failure of vancomycin in that study.

The reason I am bringing this up is I think we need to be cognizant of limitations in the data when we start talking about these. Nonetheless, clinicians have these perspectives out in practice of whether they are going to feel

comfortable using vancomycin or nafcillin or whether they are going to want to use gentamicin in combination with either one of those drugs.

The issue in a clinical trial is, again, leaving this up to investigator discretion may introduce a potential bias even though we know all the limitations of this data. So, again, could we protocol-define switches from vancomycin to an antistaphylococcal penicillin once the determination of the susceptibilities of the organisms is made.

The issue here is drawing the distinction between something that is specified in the protocol versus something that is left up to investigator discretion.

The last issue we would like to address is what would be an acceptable loss of efficacy relative to controlled drugs for this indication. Let me take a step back and, again, address something that Dr. Tally brought up. If what we are going to try to determine is is that drug effective or not, the legal requirement is you need

a control.

If what we are going to do is say, we are just to look at how patients did on our drug and compare that to some external analysis of how patients in 1942 did, that essentially is an historical control. The Code of Federal Regulations says one of the appropriate controls that you can use in clinical trials is an historical control.

But, remember, that is exactly what we have for vancomycin and we still don't know the answer for some of those questions now. So our question for the committee is would something like an historically trial be something that you folks, as clinicians, would want to see. We may get an ability to evaluate whether the drug is effective, yes or no, relative to placebo but that would probably not give us the data to evaluate how a new drug would compare to an already approved therapy such as vancomycin or an antistaphylococcal penicillin.

We would assume, though, in lieu of an

historically controlled trial, that most of these would be noninferiority trials which gets us to the issue of what would be an appropriate noninferiority margin.

We agree that that study by Skinner and Keefer actually shows a very large mortality in Staph aureus bacteremia. Again, we need to recognize the limitations of that data. That pools together patients from all sorts of sites of bacteremia including pneumonia, complicated-skin, et cetera. In 1941, there were no central lines so that is a different population of patients today than what we would have had back then. But it still argues that this can be a very lethal disease.

So the real issue here is not what is the benefit over placebo. The real issue here is what would be the clinically acceptable loss of efficacy relative to drugs that we already know are effective in this particular setting.

So the issue then is a larger noninferiority margin translates into a smaller

sample size and makes the trial easier to do. But that larger noninferiority margin also translates into more uncertainty regarding the results with that particular drug especially when it comes to comparing it to the control drug.

(Slide.)

So what I wanted to do was to sort of show you, since somebody asked the question earlier, what do the numbers actually look like, just take a second and go through some of this.

I am going to use that number of 31 percent mortality from the 2003 Chang paper and say let's just use that as the success rate in these trials. We don't know where that would be but let's just say that success rate comes out to be 70 percent.

Over here is the noninferiority margin. So the narrower the margin means the more certainty you have that the drug is effective. In other words, a 5 percent margin would say, we are going to say that this drug has to be at least within 5 percent of the control or we are not going to say

that that is useful clinically. 10 percent would be within 10 percent of the control, 15 percent within 15 percent of the control.

So what you see is that if you have a really stringent criteria of saying, we are only going to say this drug is clinically useful if it is within 5 percent of what we already have out there, that you are talking about a trial that has about 1,300 patients per arm. That doesn't count the dropout rate which may be significant in these kinds of trials so you are talking probably in the order of 3,000 patient trials.

There are only about 10,000 patients with endocarditis in the United States yearly and, given all the issues with inclusions and exclusions that Dr. Tally brought up, you have to ask whether that is even a doable thing. On the other hand, if you are willing to accept more uncertainty--namely, on the order of 15 percent--then we are talking about 150 patients per arm which, again, you would have to figure in that there would also be that issue of dropout and the not insignificant issue of

screening for these people up front as well. As Dr. Tally brought up, that is not an insignificant issue when it comes to actually trying to find people to put into the trial.

So, hopefully, this gives you some numbers to be able to frame what we are actually talking about. We can put this back up here again if we need to.

(Slide.)

So let's just go through the issues for discussion here that we would like the committee--I am going to go back to the beginning and talk about the questions that I had as the headers for those slides.

Should patients with primary bacteremia due to Staph aureus constitute a separate indication and do these patients constitute a clinically relevant group of patients that we could describe in product labeling for clinicians. Does efficacy in primary bacteremia due to Staph aureus imply efficacy in endocarditis and can drugs be studied without examining the efficacy in

endocarditis using some kind of staged approach with appropriate labeling to tell clinicians where the drug had and had not been studied?

(Slide.)

What preclinical information and information from other clinical trials would be helpful in evaluating drugs that may be appropriate for study in this indication?

What evaluations should patients have prior to enrollment or shortly thereafter to rule out a known focus of infection? Are we talking chest X-ray, echocardiogram or anything beyond that?

How should patients who develop a site of infection after randomization be handled? Should they be left on the study drug? Should they be considered failures of study medication?

(Slide.)

How should the duration of therapy in these studies be designated and what would appropriate control regimens for this indication be? Finally, what would be an acceptable loss of

efficacy relative to controlled drugs trying to balance that certainty of the results with the practicality of sample size.

Let me add on to the end of this, would an historically controlled trial be something that you, as clinicians, would find acceptable.

I'll stop there. Thanks very much.

Questions from Committee

DR. LEGGETT: Thank you, John. I know there are going to be some questions. What I would like to do--we are behind schedule--is take questions and discussion until just about noon. So please make your questions succinct and important. Tom, would you like to start?

DR. FLEMING: I have got a lot of issues and I am not ready yet to get them boiled down to a succinct summary. So I would rather go a little bit later.

DR. LEGGETT: Joan?

DR. HILTON: I will just ask one question to clarify at this point. When we are talking about efficacy, I assume that you are going to

measure that using the endpoints listed on Slide 16. You have two listed there. One is metastatic disease and one you talked about, negative cultures, or time-to-negative-cultures. Are those what you are focused on when you think in terms of measuring efficacy?

DR. POWERS: That would probably be part of the definition. We didn't want to get into today actually defining what the endpoints would be because, obviously, there are some things we left out of there, like people who die while they are on treatment.

What we wanted to say is should that be a part of the appropriate definition of endpoints. But, given all the issues we needed to discuss today, we didn't want to get into specifically defining what an endpoint would constitute.

DR. LEGGETT: Don.

DR. PORETZ: I think you are right that physicians in practice are looking for guidelines and would like specific entities. So why not, for argument sake, start out with one primary

bacteremia in and of itself; number two, bacteremia associated with a metastatic focus of infection; and number three, bacteremia associated with infective endocarditis and then start discussions from that so we have three separate categories.

I think doctors in practice would appreciate that.

DR. LEGGETT: So let's take some questions about Staph aureus bacteremia without endocarditis. One of my problems that I see immediately coming up is most of the time, even though we think we have an endovascular focus, Staph aureus is acute enough that we don't see the vegetations. A lot of the transesophageal studies are done in more subacute situations where the sensitivity is much higher.

DR. PORETZ: Don't you believe--at least it is my feeling that we tend to significantly overtreat a lot of these patients? I mean, people--based on the dogma of what we are taught, we treat for four to six weeks sometimes and people have no reason in the world to really think they have endocarditis but doctors are scared not to do

that.

DR. LEGGETT: Agreed, totally. On the other hand, we are doing that in the face of drugs with what we think have known efficacy. Here we are talking about a drug we don't even know if it works.

Alan?

DR. CROSS: I would point out that, at least based on our earlier teachings, one of the reasons that I would treat for four to six weeks is the fact that the morality with simple Staph aureus bacteremia, unquote, was almost as forbidding as with an endocarditis. Part of the reason for that is the establishment of metastatic infections. We treat for a long period of time not simply to clear the blood but to treat the metastatic foci in the spleen, kidney, wherever. That takes time.

Actually, you may recall the whole issue of teichoic acid antibodies was an attempt by the infectious-disease community to really separate out that issue to decide who may have a significant or metastatic focus that merited long-term

therapy--you can say four weeks, five weeks, six weeks--versus those who didn't.

Obviously, that is in the dust heap of unrealized tests, but the principle remains the same. I would say that the significant forbidding mortality of Staph aureus bacteremia, even in the absence of endocarditis, demands that we at least approach Staph aureus bacteremia a little differently than we do with bacteremia of other organisms.

DR. LEGGETT: I would follow up on that with this question about only leaving a 48-hour window of prior antibiotics because what you are implying is that to say 72 hours of therapy, no matter what it is, is not going to make a difference in the long run. So I think that this is different than what Dr. Powers was talking about of therapy early on and short course of treatment.

We are not talking five days of therapy for sinusitis after 48 hours. Now we seem to be talking four to six weeks.

John?

DR. BRADLEY: I think Dr. Powers has done a really nice job of detailing how complex these studies would be. He has brought up at least 20 different questions. For you to say, "Oh; do you have any comments?" I am rather paralyzed. I don't know which one to comment on first and, if I don't comment, does that mean I agree with something?

DR. LEGGETT: You have got 18 minutes.

DR. BRADLEY: So if you could go by each point that he requested, one by one, I think it would be easier for us to comment.

DR. LEGGETT: Sure. Number one; should primary bacteremia due to Staph aureus constitute a separate indication? Any thoughts? My thought is no.

DR. BRADLEY: Yes.

DR. LEGGETT: John?

DR. BRADLEY: I would agree. I think that if, the harder you look, the more you find the associated occult focus--so I would agree.

DR. PORETZ: But does that mean someone needs to be treated with parenteral antibiotics

during that whole period of time?

DR. LEGGETT: I don't think so. I think it just depend on the antibiotic. It doesn't have to be parenteral. If we have a drug that is 100 percent bioavailable with the same levels P.O. and I.V., there is no reason to give it I.V.

DR. PORETZ: I agree.

DR. PATTERSON: Could I ask--Dr. Maxwell brought up a question. You are agreeing with what? We weren't sure what you were saying. Agreeing no, it shouldn't be a primary--it should not be an indication?

DR. BRADLEY: Yes, Dr. Leggett, I was agreeing with you that primary bacteremia, itself, should not be considered its own diagnosis.

DR. LEGGETT: Any disagreement or clarifications of things? Jan?

DR. PATTERSON: I was just going to say if we are including catheter-related bacteremia in the definition of primary bacteremia, I am inclined to say yes to that question.

DR. LEGGETT: John?

DR. POWERS: Could we ask people to give their reasons why yes or no? I think, John, you said it is the complexity of actually studying it that would be--and, if the answer to this is no, what would you think would be useful in lieu of this?

DR. LEGGETT: So he is jumping ahead to another question.

DR. BRADLEY: If I can comment on Jan's question first. I think catheter-related bacteremias should not be considered in the primary bacteremias. I think if someone comes in with fever, has a blood culture and the blood culture is positive with no other associated focus--and I would consider a foreign body, the catheter, in this case, a focus--they should be considered separately.

And I forgot what your question was.

DR. LEGGETT: You have explained it. Celia, can you give some explanation about why you think primary bacteremia should or should not be a separate indication?

DR. MAXWELL: I think it would be hard to determine what primary bacteremia is because, as everyone agrees, if you look hard enough, you are going to find something. So when do you stop looking? So it would be hard for me to say what primary bacteremia is.

DR. LEGGETT: Chris?

DR. OHL: Given the complexity of the definitions and how the trials would have to be constructed in order to get this indication, I would say no. I would agree.

DR. LEGGETT: Joan, did you want to make any comments?

DR. HILTON: No.

DR. LEGGETT: Barth?

DR. RELLER: No. But Staph aureus bacteremia is, I think, much more difficult for this rubric than coagulase-negative staphylococcal associated with catheters because, without association with catheters, it is problematic. It doesn't mean that there couldn't be differentiation of persons who have bacteremia with Staph aureus

and that the indications could be different.

But it depends on the definition. Where I am coming from are three avenues. They are very familiar to all the infectious-disease clinicians here. There is a huge difference by organism in what the site of infection is. Now, I am not fast enough to do this subset analysis by Staph aureus bacteremia as well, but just to give an example.

Bacteremia with acute pyelonephritis in a young woman--I mean the bacteremia is there but that is not the issue, and there is no intervention. That is different from Staph aureus bacteremia with a phlegmon with discitis which is different from bacteremia with an intra-abdominal abscess, not with Staph aureus, or a catheter-related bacteremia with Staph aureus is very different whether it is complicated by endocarditis or complicated by osteomyelitis or a joint infection because of this issue of what are the ancillary--they are not ancillary--or the adjunctive or, in terms of outcome, the primary determinants.

For example, when we looked at all bacteremias in that thousand confirmed real bacteremia studies, on the role of removal, excision and drainage of a primary focus of infection, the associated mortality and the rank order was, if there was a removable focus and it was removed, the mortality was 6 percent. If it was a catheter-associated, sort of the purist, it was 4 percent. So it was even less.

But if there either wasn't something that you could remove or if wasn't removed--now, this is, you know, all real bacteremias, not just Staph aureus. One of the things that came out of this session is to go back and look at the cohort of Fowler and colleagues at our place. We have got now 1500--is to go back and try to assess this, the mortality--when you couldn't, it was 16 percent.

So, in other words, there is a huge effect, regardless of the bacteremia. So it is where the complication is and whether you can do something about it, and whether you do something about it. Then you take endocarditis. Let's take

Staph aureus endocarditis, treat it with a good drug that is effective, regardless of what that is. Well, the outcome is also, everyone here knows, critically dependent on if one develops a surgical complication or not and whether you have surgery.

So the real outcome depends on whether the valve is attacked, if it needs to be attacked. So it is not just the antibiotic. This confounder of prior antibiotics, I think, with Staph aureus bacteremia, given the incredible frequency of complications and especially with endocarditis, that intervention needs to be swift to preserve life but the outcome depends on some of these other things so that if you had a confounding antibiotic for two, three, four, five days, that is not going to make any difference in the outcome of endocarditis or even complicated staphylococcal bacteremia.

In other words, I don't think you would have to exclude patients. But if you take overall, and I don't have this for Staph aureus, another thing that could be done and I would like to do is

that when one looks in that, let's say, for round figures, thousand patients about the influence on mortality, attributable mortality, based on time-of-intervention, of getting the right antibiotic, the relative risk of one was you got the right antibiotic empirically; that is, you were thought to be going to be bacteremic, you got the right antibiotic--you had someone who was an experienced clinician that gave you the right antibiotic from the get-go. Relative risk of 1.

Of you didn't get the right antibiotic until the Gram stain was called, it went up a little bit but not much, 1.2. But if you didn't get the right antibiotic until susceptibility--this is taking all thousand; okay? Real--that is where the big jump came and it was about a relative risk of 3.

If you never got the right antibiotic, which is infrequent, very infrequent, it was, you know, very--I mean, it was ninefold or more. Now, this is attributable to the extent possible with a multivariate analysis, et cetera. So the point is

it makes a difference overall. I am not sure with subsets with Staph aureus it would make a difference acutely to get the right antibiotic, but the real test of antimicrobial component, when one separated out the role of excision, drainage, surgery, endocarditis, whether there is--so I think that, for me, the answer to this is complicated or not, removable focus or not and whether it was done and then that endocarditis is in a different category--this gets into duration of therapy--from the other complications.

But, even with the other complications, I think most of them are going to have four weeks of therapy and the other intervention. So it is not sort of avoiding the issue, but this maybe is really crucial and whether or not the numbers allow it to be done is something else. But I think the biggest danger is to facilely group as a primary bacteremia or catheter-related bacteremia because you have got a catheter, even if you remove it, it grows Staph aureus, et cetera, and say, okay, you can have short-course therapy.

That can be and is a catastrophe if you have not sought hard enough for the complications.

I know that is a long answer, but it is the only way you can fairly do it because these things, and I gave some numbers to show the relative importance of these other factors in making this decision.

DR. LEGGETT: Succinct, as usual.

I have trouble with a primary bacteremia because, as has been mentioned, they usually come from somewhere. So we have got to make sure that the drug works elsewhere than in the bloodstream if we are going to try to treat these upcoming complications. I think what we want to do in a clinical trial is try to avoid lumping as many things in there as possible. I think throwing a catheter-related into the primary bacteremia just makes it that much harder to group people so that you are actually sort of having some scientific looking at it.

The problem, of course, is that we are looking at the final common denominator of

something that came from many different directions. But I think that trying to look at clinical endpoints of metastasis, endocarditis, those sorts of things, as one of the outcomes is much more important to me than just whether the blood culture was negative at one day, two days or five days.

Celia?

DR. MAXWELL: This is really brief. I just wanted to comment that as John was here talking, this is an indication in adults because he was reminding me that, in children, you can get transient primary bacteremias with Staph that clear by themselves. So I am mostly confining my comments to adults.

DR. LEGGETT: Alan?

DR. CROSS: I will be brief by combining responses to 1 and 2. I totally agree with the difficulty of having a separate incident for primary bacteremia in part because, as has been said, if you look hard enough, you are more likely to find a focus.

That brings me to a second point, having

done similar types of studies, or at least in part of them, as Dr. Tally pointed out, it is very, very difficult even with something as relatively common as Staph aureus to, one, get consent within a very short period of time and, two, there is always the consideration that, by the time you get there with your new drug, that the patient has already been on some other empiric therapy.

While, in the case of Staph aureus, perhaps you still have, perhaps, more time because of the difficulty in clearing Staph aureus bacteremia and all the things that Barth pointed out, still, I think, in terms of cleanness of study, it is good to have your experimental drug started as early as possible.

So, in thinking about this, I would just like to, perhaps, ask Dr. Fleming to comment either now or later about a type of approach that we have had at least in the cancer and infectious-disease field where you often will have preemptive or even prophylactic antibiotics. So, clearly, if a patient comes to an emergency room and there is a

high suspicion of Staph aureus bacteremia, the physicians will start antimicrobials even before the patient hits the floor.

So I am just wondering about a type of design in which a patient is randomized at that point and then you actually embed into your study a subsequent workup which may include as much imaging as Dr. Powers pointed out or your echo and at least have that already built into your study so you have already prospectively defined these more complicated cases and how you analyze them.

But, in the meantime, what that does is it allows you to get your drug on board much more quickly and also to allow the 48 hours, at least to obtain informed consent which is really a formidable problem.

DR. LEGGETT: Tom, do you want to make a statement?

DR. FLEMING: I actually would want to get to that. I am going to defer. There are two or three other critical questions that I would like to have some time to talk about and that point comes

up in one of those later questions. So, just to be brief on this one, I am very persuaded that, with the diagnosis of Staph aureus bacteremia, it is very important to do everything possible that is practical to achieve knowledge about the site.

The site clearly has a lot of influence on our projected efficacy and outcome. The challenge, as I understand it, is in maybe 20 percent, we are not going to succeed in that, at least within the time frame that we have available to us. So where are you left with those 20 percent? I understand that this primary bacteremia category is basically those for whom we haven't been able to identify a primary site except maybe catheter-related.

So what do we do with this 20 percent? I am endorsing all the comments that we would certainly want to understand site if we can and that would then be how we would characterize those people. But what do you do in the 20 percent if you don't consider them a separate indication?

DR. LEGGETT: Jan?

DR. PATTERSON: I was just going to

explain my yes, as requested. I guess it is my hospital epidemiology hat since I have been doing that for 15 years. I am very comfortable calling a catheter-related bacteremia a primary bacteremia. I think it is a distinct clinical entity and it has different implications than other catheter-related bacteremias which we treated differently.

I agree that the reasonable amount of workup needs to be done, which we usually do for Staph aureus catheter-related bacteremia to make sure that it is nothing else.

DR. LEGGETT: Nate?

DR. THEILMAN: So this is a difficult issue. I worry that, if we split things up too much, we are not going to be left with anything to study. So, to some extent, some lumping may be required. Of course, attendant with that is the risk of heterogeneity in the population that we seek to study and invalid results.

Dr. Powers, in his third slide, has given a definition for primary bacteremia, evidence of systemic signs and symptoms with positive blood

cultures for Staph aureus and no identified source of infection at time of enrollment.

I think, if we prospectively figure out how we are going to try to identify sources of infection at that time, and that could range from including a transesophageal echocardiogram to tagged white blood-cell scanning as was done in one of the studies present. This might be doable. I would not advocate, by the way, for tagged white blood-cell scans in everyone but I think I would for a TEE.

DR. LEGGETT: Don?

DR. PORETZ: Maybe I disagree but I really think there is an entity of primary Staphylococcus aureus bacteremia. I have seen a number of individuals. I have looked and looked for a focus. I can't find a focus. They had the mucous-membrane break or a skin break and that is how the organism got into the blood culture.

If you can't define that as primary bacteremia, I mean that is what it is. I am not sure those people need to be treated--they do need

to be treated, but I am not sure--in 24 hours, many of those people are better on therapy. I am not sure all those people who are better in 24 hours need to have, because of the potential to have a valve infection or a metastatic focus of infection--need to have a very, very prolonged course of therapy.

DR. LEGGETT: John?

DR. BRADLEY: You bring up an excellent point. If you find Staph aureus in the bloodstream, you go after what might be the primary site you and investigate them. As was brought up earlier and in John's definition, now obvious secondary site at the time of enrollment. We all know that chest X-rays, echos, can all become positive after your first evaluation.

So building into a protocol the points at which a repeat evaluation would need to be made and how detailed that repeat evaluation would need to be are important to decide because you are right; many of them get better but there could be just a mild infiltrate that clears with oral therapy in a

subset.

DR. LEGGETT: Chris?

DR. OHL: I was just going to, I think, clarify some of what we have all been saying also. What is different is would a clinician find such an indication useful. I would say to that, yes, they would find that useful. But, unfortunately, it is such a complex issue in trying to show what primary bacteremia is. At this point in time, with our current technology, may not be well definable enough to answer the question that the clinician wants to know.

The other thing that struck me and I know Barth and others have been thinking about this for a lot longer than I have in these types of settings, but clinicians, I think, are much easier to take information that is shown that the difficult situation, the more difficult diagnosis, the more difficult infection, if there is efficacy there, they are much more willing to extrapolate it back to more simple situations.

So realizing that the numbers that we are

going to need to get clinical trials to study the more complicated bacteremias, and the most common complicated, I guess, would be endocarditis, we would need much time, not only to get the trial done but also to have enough clinical acumen and experience with what is it there for lesser indications in order to go for that.

So I think that is my understanding of the complexity of the issue. So the question you initially asked is that, if our technology was there, in order to completely define what that is, the answer would be yes. But I am not sure that our technology is there right now for us to be able to define that to make that trial doable.

DR. LEGGETT: If I understand you right, what you are saying is that you would want to feel comfortable in the most complex situations. In other words, you would first like to see the drug work in endocarditis and other complicated bacteremias before you went down to Don's simple one which is the exact opposite of what they were talking, if I understood correctly today, the

stepwise approach which was going from the simple to the complex.

Barth.

DR. RELLER: From a clinical standpoint, actually, I am in complete agreement with Don. The question is how to safely separate those. So one possibility, and I could envision this as doable--one possibility would be to have a category of uncomplicated primary bacteremia and then a complicated bacteremia that would encompass endocarditis that has other set of considerations.

But that an indication not be given for complicated, necessarily; in other words, that it wouldn't be either/or because you have to sort out the endocarditis and there may be an endocarditis indication. There may be an endocarditis indication and a primarily uncomplicated indication. Then you could say, well, what about the others.

Well, I think the others, the outcome, is actually also very much dependent on what you do about that complication. So getting to that

uncomplicated primary that would include a catheter that was removed would be something that you come to by exclusion of complications.

One of the things that I think is a real plus on the studies that Dr. Tally presented, or the study in progress, was this concept of you can't just say it is uncomplicated and start something and ignore them. But you are watching them like a hawk. You are making sure that you don't miss something. And you are following them for a long enough time to see what came back to bite you that you missed, this "seek and ye shall find," usually--not always, depending on how hard you go.

So I think that it is not that it is impossible, but it is the care with which it is done because I think, from a clinical standpoint, the uncomplicated bacteremia with Staph aureus is a reality that would not necessarily mandate for everyone for six weeks of therapy.

DR. LEGGETT: Let's jump to the last slide because it is now--by the time we finish, it will

be quarter after 12:00. Tom, do you want to address those issues?

DR. FLEMING: All right. Actually, what I would like to focus on, just to drill down, is on two issues, the last issue on Slide 22 on our handout and the last issue on Slide 23.

The last issue on Slide 22 is should patients who develop a site of infection after randomization be handled. There were several questions during John's presentation that led up to this summary question. To address this, I am going to, in fact, propose what I would think would be the kind of information I would want to look at as outcome because it sets up my answer.

In this setting, what we are looking for--certainly, one component of this would be negative blood cultures. But we know that is not enough. That certainly isn't sufficiently predictive of what is happening at primary sites. We would also want to look at complete resolution of entry signs and symptoms.

But, from my perspective, in particular,

the elements that I would really hope for as being affected with an effective antimicrobial here would be to reduce some of the more particularly serious sequelae, to reduce the risk of mortality, to reduce the risk of metastatic infection or infective endocarditis.

So, if someone, post-randomization, develops a metastatic infection, that is an outcome. That is not a subgroup-defining characteristic. So, if we were to pull those people out of the analysis and do subgroups, then we are missing the fact that the occurrence of these post-randomization events could be part of the signal of the effectiveness of the antimicrobial intervention in preventing or reducing the risk of these events which comes back to the principle that intention-to-treat analyses are really critical if we believe in the importance of randomization.

Randomization gets rid of systematically occurring imbalances but only if we, in fact, include all randomized people in the analysis.

Now, in the need to randomization and initiate therapy before all baseline insights are in hand, one could envision that certain samples could be obtained that would be analyzed in the next 48 hours. One could state that if those samples were taken at randomization, then the intervention didn't influence the outcome and analyses could be done that did and didn't include those patients.

But those are different from the cases where post-baseline information is used to exclude patients because of events that occur post-baseline.

So, in essence, I would argue that, to preserve the integrity of randomization, if there are infections that occur post-randomization, those are outcomes and those people should be left in the analysis as outcomes. It does mean, though, as a result, it is very important for us to do the very best diagnostic assessments as practical at baseline so that preexisting conditions can be identified and not need to be included as outcomes

because those that aren't found are, then, obviously going to dilute the assessment of efficacy.

Nevertheless, unless you can tell me that you know for a fact that what is found after randomization was present at randomization, then we could missing part of the signal of treatment effect by excluding those people and not counting those events as outcomes.

Moving to the last question which was one relating to in a setting where you have very effective active comparator interventions on endpoints such as mortality. Now you are assessing a new antimicrobial. What is an acceptable margin? Dr. Powers was giving us slides that were referring to the setting where you had maybe a 30 percent mortality rate.

The question is, now you are going head-to-head against that comparator and intervention. Clearly, we know, in this setting, that this intervention has a profound effect on that endpoint. In the absence of the comparator,

mortality rates would be very much higher than 30 percent.

But the driving issue here in ensuring that you don't have too large a margin comes down to what is clinically acceptable for how much higher mortality risk would you allow. He gave what might be viewed to be some compelling arguments for allowing a big margin.

If you allow a 15 percent margin, if you say, I just need to rule out the mortality at 30 percent is not increased to more than 45 percent, you might be talking about sample sizes of 150 per arm while, if you were talking about ruling out a 5 percent increase, you might be talking about sample sizes that are tenfold that large.

The difficulty, though, is how much are we willing to allow in truth clinically, in terms of lesser efficacy. If we are lenient in allowing considerable flexibility here to accept small sample sizes, then, when we get a second generation intervention that maybe, in fact, truly does have a 40 percent mortality and we now use this as our

active comparator, how many iterations of noninferiority trials are we going to go through before we have the risk that we are now accepting interventions that have truly a substantially higher mortality rate.

So when I think if what is the margin that we would allow, I just turn the tables around and say, suppose, in fact, 45 percent mortality was the standard and you could come through with an intervention that would reduce that to 30. Would that be an important advance? You bet it would. You bet it would. So why would you allow that big a loss of efficacy?

If you had 40 percent mortality and you could reduce it to 30 percent with an experimental antimicrobial, would that be an important advance? I would suspect strongly that it would. So, to allow for remarkably large margins, based on artificial motivation that is statistical to get small sample sizes, can compromise the best interest of public health in patients.

In reality, I argue that the sample-size

picture that Dr. Powers put up, while accurate, might not, in fact, be that burdensome in the following sense. If those calculations were all based on the assumption that the experimental is no better than the standard, if the experimental is slightly better than the standard, then you can rule out that you are modestly worse with much smaller sample sizes than were shown here.

So what it means if, if I am not improving public health, yes, it does take a big sample size to rule out that I am taking a step back. But if I am actually providing a very modest improvement, not enough of an improvement that I could show is statistically significantly superior, but a modest improvement so I could rule out I am modestly worse, that is an important advance and that can be assessed with a much more modest sample size.

Final point and that is historical controls. Can you use historical controls? If we do an uncontrolled trial, it truly is controlled. It is controlled by our best sense of how these patients would have done in the absence of our

intervention. It is an historical control.

When can you use those? You can use historical controls when you have a very clear idea of what the result would be in this population in the absence of your intervention and where you are looking for really big effects. Well if, in fact, we said the margin that we, in fact, would accept here would be 5 to 10 percent on mortality, meaning that the comparator is going to have about a 30 percent mortality, we want to know that we don't have more than a 35 to 40 percent mortality.

But I don't want to do a controlled trial, randomizing half these patients to the control arm. I want to use historical controls. It is treacherous. To be able to distinguish an observed mortality rate of 35 to 40 percent and to be able to conclude that that, in fact, truly reflects benefit, that this would have, in fact, been 30 percent, means you have to have a highly homogenous, highly predictable setting.

Everything that I have heard today says, no way. There are an awful lot of factors out here

that can influence outcome. It is exactly the circumstance where I cannot use an historical control, where I have a lot of heterogeneity and I am trying to discern modest differences on critically important endpoints. I have to have a proper randomized comparator.

DR. LEGGETT: Thank you. I think we will adjourn for lunch. We have to be back here promptly at 1:00 for the Open Public Hearing.

(Whereupon, at 12:20 p.m., the proceedings were recessed to be resumed at 1:00 p.m.)

A F T E R N O O N P R O C E E D I N G S

(1:15 p.m.)

DR. LEGGETT: We are going to open the afternoon session with the Open Public Hearing for which we have two known speakers and we will see if anyone else wishes to speak.

Open Public Hearing

DR. LEGGETT: First of all, I need to make this statement. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such a transparency at the Open Public Hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first speaker at this session is going to be Dr. Tim Henkel.

DR. HENKEL: Thank you, Dr. Leggett, and thank you to the agency for the opportunity to address the committee today.

(Slide.)

What I would like to do, since I have the much sought-after after-lunch spot here, I will keep my remarks brief, is describe our experience with a catheter-related bloodstream-infection study conducted according to the current guidance.

What I won't do, since it has been done by

others and that conversation will be continued this afternoon, is talk about medical need, talk about epidemiology of disease, talk about statistical considerations because I think those have been well covered.

I am going to focus on study design and conduct of the study. Even though this study is completed, I also won't talk about results here today. It has been presented in part at the European Congress of Clinical Microbiology and Infectious diseases and will be published in full in an upcoming issue of Clinical Infectious Diseases. So I would like to focus on the design issues.

(Slide.)

This is a Phase II study, a randomized, controlled, open-label study of dalbovancin, a new lipo-glycopeptide antibiotic under development administered once weekly compared to vancomycin administered twice daily.

The study used clinical and microbiological entry criteria, which I will

describe further, consistent with the draft guidance for CRBSI. The primary endpoint of the study was the global response; that is, the combined clinical and microbiological outcome at the time of a follow up visit some two weeks after the end of therapy.

The sample size planned here was about 60 patients per group. This is a Phase II study with descriptive statistics only, 95 percent confidence intervals planned around the point estimates of success.

(Slide.)

The inclusion criteria utilized documented Gram-positive bacteremia at baseline which is how most patients were entered into the study. We did allow for empiric enrollment of patients with signs and symptoms of bacteremia, basically signs and symptoms of the systemic inflammatory-response syndrome, fever, hypothermia, leukocytosis, leukopenia, or a left shift in the white count, tachycardia, tachypnea or transient hypotension.

(Slide.)

We excluded patients, consistent with guidance, who had received more than 24 hours of antibiotics for that episode of Gram-positive infection. We excluded patients who had a documented alternate focus of infection identified at the time of randomization.

We also excluded patients who had recent Staph aureus bacteremia with a documented source other than a central venous catheter out of concern that it was actually a recurrence of that alternate source rather than a new bacteremia.

We included patients only for whom a two-week course of antibiotics or less was deemed to be appropriate. Creatinine clearance of less than 50 or neutropenia, these largely were the results of the phase of development we were in with the compound at the time and, as Dr. Tally mentioned, not knowing what the appropriate adjustments for renal insufficiency were at the time.

We also excluded patients on chronic immunosuppressive drugs or with organisms with

documented resistance to either of the study drugs.

(Slide.)

In terms of microbiological methods, I think Dr. Murray outlined a few of these already this morning. We did catheter cultures where catheters were available for culture, either roll-plate or sonication techniques. We looked at time-to-positivity of catheter cultures versus peripheral cultures when that data was available at a given site.

We also looked at quantitative cultures again where sites could conduct that analysis, cultures of exudates at insertion sites and then, for organisms other than Staph aureus, looked at antibiograms and, to confirm identify of paired isolates, pulsed field gel electrophoresis.

(Slide.)

In terms of the outcome definitions, clinical outcomes were defined as improvement in signs and symptoms such that no additional therapy was required. So, in this case, a metastatic focus of infection would have been identified after two

weeks of therapy. The patient would have required more therapy and would have been classified as a failure.

We looked at microbiological success or failure simply as clearance of blood cultures as success, persistence as a failure.

(Slide.)

We developed several classes of catheter-related bloodstream infections for purposes of analysis. A definite catheter-related bloodstream infection, per guidance, was defined as one of the following; at least one positive peripheral blood culture plus either a positive semi-quantitative catheter-tip culture; a quantitative catheter culture or a positive hub or tunnel exudate culture.

It could also have been more than a five-fold increase in the colony-forming units per ml of an identical pathogen from a central versus a peripheral culture or where sites could conduct the analysis again, a more than two-hour time lag in the time-to-positivity for the peripheral culture

relative to the central culture.

(Slide.)

There was an additional category of probable catheter-related infection. So, for Staph aureus, at least one positive peripheral blood culture in the absence of other sources of infection in addition to a physical examination, chest X-rays, urine cultures, and then any imaging directed by the physical examination of other signs and symptoms.

Patients also had an echocardiogram. A transesophageal echo was strongly recommended although we would accept a transthoracic echocardiogram. Those could actually be done after the randomization decision. So it was possible with the design that a patient with endocarditis could have been randomized and would later have been classified as a failure. That, in fact, did not happen.

For other organisms such as coag-negative Staph, we required two positive blood cultures as I have described already, at least one of those

peripherally.

(Slide.)

We opened 34 centers in North America and enrolled the study over a period of 17 months. Just over 2,600 patients were screened, and I will give you the reasons for the screen failures in just a moment, to enroll 75 patients. So we fell short of the 60 patients per arm that we had hoped to enroll but chose to close enrollment at this point.

(Slide.)

In terms of reasons for screening failure, the most common was inadequate culture data. In large measure, this reflected the difficulties with getting the culture data for coagulase-negative Staph. So some of these are certainly the patients we have talked about this morning with a single positive culture who probably don't have disease.

The second most common reason was prior antibiotic usage. This excluded patients with both coag-negative Staph as well as Staph aureus but, in fact, is more problematic for the Staph aureus

patients. I might also add that these reasons are not necessarily mutually exclusive. This is the reason listed first for screening failure.

I talked about renal insufficiency already. 13 percent of the patients screened had an alternate focus of infection identified prior to randomization. Patients were also excluded if they had mixed Gram-negative and Gram-positive infections or if they were neutropenic.

(Slide.)

So, just to conclude, the difficulties in conducting the study and the reasons that patients couldn't get in. Identifying patients with Gram-positive bacteremia, as you all well know, is easy. There are lots of them. Some of them clearly don't have infection, in the case of coag-negative Staph. The population was quite heterogenous. I think the inclusion and exclusion criteria applied per guidance--this is slightly more liberal than the guidance, not more strict--I think result in a population randomized that may not be representative of the disease spectrum. So

the generalizability of the data, I think we have to question.

The microbiological methods that are dictated by the guidance are really not standard in many hospitals, the time-to-positivity of cultures or the semi-quantitative cultures. Catheter-tip cultures are actively discouraged in many places today.

So our conclusion was that a Phase 3 study with the current design really was not feasible. I think we badly need alternate approaches to bacteremia indications, different study designs. My personal perspective is that I would rather not see us lump coag-negative Staph with Staph aureus. I understand the rationale for the guidance in terms of insuring that a coag-negative Staph is really a pathogen. I think that is appropriate. But I think it eliminates patients with Staph aureus that truly do have infections.

One of the things that already has been mentioned today in terms of exclusions that would help enroll patients with Staph aureus bacteremia

in trials, and that is simply relaxing the time frame that one allows prior therapy before the randomization decision.

It does a couple of things. It allows you to get culture data back from laboratories and confirm that it is really Staph aureus, number one. It allows you to do a little more of an evaluation for other foci of infection. You can get the echocardiogram done and, in fact, doing echos or even transesophageal echos, in the United States in a short time frame really was not terrible difficult. It allows you to get a CT scan if you need one, for that matter.

So, from my point of view, I would urge the committee not to continue with the current guidance that looks at both coag-negative Staph and Staph aureus in the same kind of indication but to entertain an alternate design that found a way to look for Staph aureus bacteremia.

Thank you.

DR. LEGGETT: Thank you very much.

Are there any questions?

Don?

DR. PORETZ: I understand. It is obvious the difficult in doing these studies and the low number of patients that are enrolled, but I have a separate question. Of the 70-some-odd patients that you enrolled in the study, how many had Staph aureus in the blood?

DR. HENKEL: About half of the patients with the baseline pathogen had Staph aureus in the blood.

DR. PORETZ: So if 35 or so had Staph aureus in the blood and you eliminated those with metastatic foci of infection and those with endocarditis because you had a two-week--you only gave two doses.

DR. HENKEL: Correct.

DR. PORETZ: One dose a week for two weeks.

DR. HENKEL: That's correct.

DR. PORETZ: Of those patients that were enrolled, those 30-some-odd patients who had Staph aureus in the blood, as they were followed after

the study ended, because I am sure you had follow-up study. They were followed for X period of time. Vis-a-vis our conversation this morning when we talked about 35, 50 percent incidence perhaps of metastatic focus, what percent of those 35 patients had, after two weeks of therapy, a metastatic focus of infection that you could prove three or four weeks after the drug was stopped?

DR. HENKEL: With this small sample size, none of the patients had a demonstrated metastatic focus during the follow up.

DR. PORETZ: How does that go with what we discussed earlier this morning?

DR. HENKEL: Well, I think the screening procedures used, the echocardiograms, the physical exams, chest X-rays, urine cultures, did exclude some of those at baseline, because the other way to ask it is a little less objective. But the investigator, at baseline, needs to believe that two weeks of therapy is going to be adequate for that patient.

So there is a little bit of clinical

judgement in there. If the patient has back pain that is new and on palpation of the disc, that patient didn't get into the study.

DR. LEGGETT: Any other questions?

Thank you so much.

Our next speaker will be Dr. Charles Knirsch.

DR. KNIRSCH: I am Charles Knirsch and I am employee of Pfizer's. Thank you.

(Slide.)

I would also like to thank you, Dr. Leggett, and members of the advisory committee for the chance to talk a little bit about some of the issues we have had in conducting a catheter-related infection study.

(Slide.)

A very common site in ICUs in this country and elsewhere, but I think it is clear that we all, and this committee has been working on trying to find ways to find evidence of antimicrobial efficacy and safety in this patient population.

(Slide.)

This was reviewed earlier. The size of the problem is large. There is significant morbidity and mortality. I think because of the difficulty and how sick these patients are, there should be a way to get antimicrobial efficacy studies done in this patient population.

(Slide.)

We have an ongoing trial so I do not have results but I would like to talk a little about some of the issues. I will try to focus on thoughts related to the incident because this trial is a Phase III trial very similar to the Phase II trial that Dr. Henkel described, very much consistent with the CRBSI Guidance from 1999.

We do have pooled microbiology because a central lab is being used. So, in the 600 patients enrolled to date, nearly 100 patients have Staph aureus both from the catheter site and from peripheral blood. So that is the easy territory, I think.

Slightly less than that have Staph aureus from one of the different catheter components,

either from a blood draw, a cath-tip culture. And then, moving into coag-negative Staph, you can see that the numbers are actually smaller which actually we are quite happy about but still, with about 38 patients that have coag-negative from both the catheter and peripheral blood.

(Slide.)

This study wouldn't have been conducted had we not had some preliminary data in the organisms that would be involved, so data from methicillin-resistant Staph aureus, from VRE and, actually, a pediatric study that had a number of patients that were enrolled that actually turned out to have catheter-related infections.

I think particularly important was a complicated skin study of good power that was in the original Phase III database. This gave us the basis for moving right into Phase III in a catheter-related study.

(Slide.)

So, looking at what potentially is the primary endpoint for which the power calculations

would be based on is the issue of concordance, so the paired specimen from the catheter and the blood. Using the assumptions, actually, in one of the scenarios that Dr. Powers showed, note the delta of 15 which some people think is a little bit large, especially, maybe, for the coag-negative Staph, maybe not for the Staph aureus, an equivalence trial would need 147 evaluable patients per arm.

To get to those evaluable patients with the microbiology rates I showed you, with about 30 percent of patients being evaluable, you are actually getting close to 1,000 patients. The current guidance asks for two studies to be done.

(Slide.)

We have also had slow enrollment in the study, at times less than 20 patients per month. So we did a bit of an audit on the U.S. sites to see what were the problems with the screening failures. Now, remember, we have not analyzed the study. This is just that the patients did not make it into the study.

Our rate of entry into the study was about 7.6 percent. The top five reasons were driven, actually, by the first two at about 20 percent each was previous antibiotic treatment for greater than 24 hours, infection that turned out not to be catheter-related when assessed by the study team. Then other causes, leading causes, were bacteremia that did not turn out to be a Gram-positive pathogen, a catheter actually being removed before the study team came to evaluate the patient or, in fact, no signs of catheter infection.

(Slide.)

So, as it turns out, with our current rate of entry, we would need to screen just over 25,000 patients to enroll both of these studies. That is a lot of patients. I think everybody knows that and it is at a rate of entry that is unlike any other trial that we do in anti-infectives.

(Slide.)

I think some of the ways to make these studies more feasible would be to allow greater than 24 hours on any staphylococcal therapy. So I

think I heard some glimmers of hope along that line in the discussion this morning, at least for Staph aureus. I don't think 48 hours of Staph aureus therapy is going to prevent metastatic complications. Do we have data that shows that? Yes; actually, we do have data that shows that actually sometimes 10 to 14 days of therapy is not enough. I don't know whether 48 hours is different than 24 hours, but we would liberalize that. That has been confirmed, actually, by some of the physicians on our steering committee for the study. They think, actually, the enrollment would double just by changing that criteria alone to 48 hours.

We could talk a long time about the different criteria for Staph aureus. The only point here to make would be that I think that if we are drawing Staph aureus out through the peripheral catheter in a patient that is sick and you rule out other causes that, potentially, you would consider that patient evaluable.

Then there is the argument about whether

to separate the coag-negative Staph. If you do that, though, and you are just looking at Staph aureus, the numbers are rather large. I mentioned originally to do a Phase III study in this indication, we had data that were organism-specific but also a large study in complicated skin.

So I would argue that one adequately powered study when you have supportive data in a relevant indication, and there are other relevant indications, but I will point out at least complicated skin, that that should be considered by the committee.

(Slide.)

So just backing up a little bit on definitions. If you look at the IDSA guidelines and start working with a definition for CRI, one could say, or work with this, that it is an infection that involves a catheter at any point including the intravascular subcutaneous or the exit-site portions.

Then a catheter-related infection actually may or may not be accompanied by bacteremia for a

variety of reasons. There may have never been bacteremia. There may be bacteremia that is not picked up by the techniques that are involved either by the team that was drawing the cultures, the laboratory processing, delays in processing, et cetera.

(Slide.)

So the catheter, itself. There are multiple ways that this can be made manifest; a frank septic phlebitis, an exit-site infection, a tunnel infection, a pocket infection or a catheter-tip infection which would not be a soft-tissue infection, actually. Any of these phenomena can lead to a blood-stream infection.

(Slide.)

This is modified from the advisory committee meeting in October of '98. We took certain liberties with it which was to place the CRI definition I gave within complicated skin and soft-tissue infection. So I added the C because most of these CRI patients will have systemic signs, or clinical signs of systemic infection. So

that is why I do think it is complicated. Whether it is complicated or uncomplicated, I am not too worried about. So we do see it as a subset of skin and soft-tissue infections.

(Slide.)

I can see this pretty well on my screen. Hopefully, you can see it on the board. But this is clearly somebody that has a catheter-related infection. I think most of us would pull this line and start antibiotic therapy right away. We won't find out for 24 to 48 hours whether or not this patient is bacteremic.

I think this is a patient worth studying in antimicrobial trials and looking, also, at the bacteremia but not, necessarily, looking at the bacteremia as the primary endpoint.

(Slide.)

So, in summary, as I mentioned, I think that a well-powered CRI study complementary to an existing relevant indication addresses the medical need for a drug approval for CRI. We are always caught between the guidelines that come out and

actually operationalizing the guidelines and implementing them. I think that remodeling the process, at least having a chance to be part of the dialogue, is a good thing and I see that the guidelines--it looks like there is an effort to evolve these. To make the indication more practical is a good thing and, hopefully, will allow for future innovation and anti-infectives in these areas.

Thank you.

DR. LEGGETT: Thank you.

Are there any questions? Dr. Knirsch, obviously we would all agree with the photo that you showed that there was an infection there. Short of that, how do you have a hard endpoint and at what point do we go down the tricky slope of getting Staph aureus through a culture of a catheter and then not really knowing if the person is sick or not, or even if they are infected or not.

DR. KNIRSCH: I think, ultimately, what it comes down to is whether you need the paired

specimens in bacteremia to be the primary endpoint that you power the study off of. If you want definitive proof with deltas of 5, that is obviously the best evidence. But if we are basing treatment decisions to add gentamicin to nafcillin based on 11 patients or what not, you have to weigh the relative amount of data you have.

We also have catheter treatment guidelines based on almost zero data, as mentioned in the briefing document. So I think what is needed is incentive to have people do these studies with a wide variety of antimicrobials.

That being said, I don't think anybody would leave that patient, even if you know, a priori, that they were not going to be bacteremic, with antimicrobial therapy. So treat it as a complicated skin infection, decide what amount of bacteremia data you need but not as the primary endpoint that would be meaningful--be evaluated by practicing physicians.

DR. LEGGETT: I see that, whether or not there is bacteremia, that is one end of the

spectrum. What I am worried about is the other end not really being real.

DR. KNIRSCH: I think you have to depend on the quality of investigators at academic centers somewhat. When you need 180 investigators to get these types of studies done, then the quality may dip off. But there are 180 good sites that can do these studies. I think most of these investigators know, or at least with a pretty good amount of specificity, when somebody has catheter infection.

Are they wrong sometimes? Absolutely.

DR. LEGGETT: John?

DR. BRADLEY: I have a question about the natural history of catheter-related infections in adults. Certainly in pediatrics, we are more conservative and tend to treat even after the catheters are pulled. In conferences where you and other adult ID colleagues are present, I understand that it is much more often that, once you pull the catheter, you basically don't continue antibiotics, particularly for coagulase-negative Staph.

I get nervous just looking at the picture

that you showed. We would certainly pull that catheter. My question is, in the adult world, if you have Staph aureus that is causing that subcutaneous infection, whether there is bacteremia or not, if you pulled that catheter, would you continue to treat that patient or would you think, since the catheter has been pulled, that the patient is likely to spontaneously resolve their local inflammation and, as a parenthetical remark, to differentiate between Staph aureus and Staph epidermidis or the coagulase-negative Staph.

The systemic systems, the degree of fever, degree of white count, in our experience with kids, is vastly different. The amount of local inflammation is vastly different.

Thank you.

DR. LEGGETT: I would think there is a variety of opinion. But there is at least a large minority opinion that, if it is coag-negative Staph, you just pull the line and let them go. With Staph aureus, you have got about 50/50 chance with Gram-negatives and Candida that you have got a

0 percent chance of cure without pulling the line.

Oh; that guy gets his line yanked. That person gets their line taken out.

DR. BRADLEY: And antibiotics.

DR. LEGGETT: And antibiotics.

DR. BRADLEY: Okay; that was my question.

DR. LEGGETT: But not for four weeks.

DR. BRADLEY: Okay.

DR. LEGGETT: Chris?

DR. OHL: Just a point of clarification. In putting the indication for catheter-related infections complementary to, say, skin and soft-tissue which was the example, would that, then, just be those components of catheter-related infections that had a skin and soft-tissue inflammatory component and, within that subgroup, would you include exit-site infections also or just tunnel infections?

DR. KNIRSCH: That is a good question because I think that coagulase-negative Staph is often a colonizer and then causes infection on the catheter tip. So I think it is a different

problem. I think that there is a fair amount of suggestion in the literature that, even when you don't know and you are desperately short of additional sites to put the line in, because changing a line over a guidewire is not a particularly good idea, either, that some people will risk treating to the line waiting for evidence of the cultures.

But Staph aureus, people will pull the line at that point. If it is coag-negative, there are efforts to treat the line. That is a whole other line of study that could be propose, actually. So I think that, scientifically, it would nice to separate Staph aureus and coag-negative Staph. Absolutely. I agree with that. And the studies would be very different.

Practically, to get a study done, I am recommending treating the syndrome of CRI.

DR. LEGGETT: John?

DR. POWERS: Could I ask Chuck a take-off question from that. On your Slide 11, you listed a number of these catheter-related infections. The

last one is catheter-tip infection. Could you define more clearly for us what that actually is?

DR. KNIRSCH: I think, in most cases, that is coag-negative Staph. So I think it is somewhat different. If you were going to split these apart, I would recommend that that would be more of a coag-negative Staph type of study, maybe treat through the line with combination therapy.

DR. POWERS: So that is just colonization of the tip of the catheter without any other signs and symptoms?

DR. KNIRSCH: No, no, no. First of all, all of these patients, if they don't have obvious sign of catheter infection have some signs and symptoms, high white count, tachypnea, those types of things. So they need to be sick with some suspicion.

I think, in practice, what is going to happen, if you expand out to 48 hours, good clinical-trial groups will be monitoring the microlab looking for Gram-positive cocci in clusters and then enrolling those patients in

studies. I think that is a good way, actually, to get these studies done.

DR. LEGGETT: Any further questions? Thank you, Dr. Knirsh.

DR. FLEMING: Maybe just one?

DR. LEGGETT: Oh; sorry, Tom.

DR. FLEMING: Your primary endpoint focused on the microbiological element. Certainly there is some uncertainty about whether that is adequate consistent with what the actual clinical effects will be. Did you believe that the sample sizes would be a lot larger to be looking at a more global endpoint, an endpoint that included clinical elements?

DR. KNIRSCH: Well, first, let me comment about, if you were suggesting this morning that we should get a one-tailed test and do noninferiority studies, I think that that may be a potential option here. I mean, we tend to do two-tailed tests of equivalence always. So that may be one way, and I think that is what you were saying this morning.

I think, with bacteremia, you need to prove that the bacteria is gone. I supposed that plus a clinical response is also important and that is what you will get. In the MITT population, that is what you will get. And then the microbiologic evaluable populations.

DR. LEGGETT: Barth?

DR. RELLER: I would like to come back to the clinical picture with the tunnel infection. The way for clinical trials as well as clinical care, I would assess that if the blood culture were obtained to the catheter and was positive for a staphylococcus and there was no--excuse me--staphylococcus demonstrated there were no positive blood cultures, it would qualify as a skin and skin-structure infection but I don't see how you could ever categorize it as a CRBSI.

If it were Staph aureus and there was a positive blood culture through the catheter and one peripheral, I would not think it is necessary with the same, and an antibiogram with Staph aureus, given the relative pretest probability that it is

going to be real, that one would need pulse field gel electrophoresis. But you would still need, through the catheter and peripheral, at a minimum, or two peripherals.

In contrast, if this were a Staph epidermidis, which it could be, one would need, at a minimum of through the catheter and a peripheral and that they would be the same by pulse field for clinical-trial purposes given the much lower pretest probability that--in other words, through the catheter only with the Staph epi, I don't think that is enough. If you don't have a positive blood culture, I don't see how you could ever enroll a patient for a CRBSI clinical study.

DR. LEGGETT: Alan?

DR. CROSS: I would agree with that Barth. A real problem is with, again, as was pointed out here, your cancer patients who have a large portion of the chronic indwelling catheters, who do get a lot of the coag-negative Staph infections, oftentimes their low platelet counts, actually, unfortunately, preclude a peripheral culture.

So when you see these patients, especially in things like triple lumens, you get all sorts of I guess we heard the word this morning urban legend, about whether one, two or three portions of a triple lumen are positive in the absence of a peripheral culture, whether or not that is significant or not.

So I agree with what you say but then what that would mean is that a significant population that, I would imagine, we would be interested in would be left out of the studies.

DR. LEGGETT: Janice?

DR. SORETH: I think what we are getting at here is the idea, perhaps, Dr. Reller, that you might think in terms of a patient population and an indication that would read something like catheter-related infections with or without bacteremia.

Clearly, patients who were not bacteremic would not fall under a CRBSI. But I think there may be the potential to look at this patient population with the semantics that I just said,

don't know entirely but it has merit and is one of the issues on the table.

DR. RELLER: The reason why I mentioned it is obvious is there is a body of literature, particularly from Europe, that is emphasizing CRBSI with negative blood cultures. I think, for clinical trials, that is not possible to objectively study.

DR. SORETH: Correct. And that is not the path we are going down. At least, I don't think it is.

DR. RELLER: But others have gone that way.

DR. SORETH: That is Europe.

DR. LEGGETT: Are there any other speakers here who would like to say something during the Open Public Hearing? Yes, sir.

DR. SHLAES: I am David Shlaes. I am from Idenix Pharmaceuticals. We actually currently don't have any antibacterials in the clinic or preclinic, but I will try and make a few comments anyway.

First of all, just to put things in a little bit of perspective, 80 percent, based on a number of studies, of antimicrobial usage in hospitals is for empiric therapy. Empiric therapy, right now, is not--there is no indication for empiric therapy. Our regulatory agencies have no direct input in educating physicians about empiric therapy.

The way the industry approaches this is to try and get many indications that are regulated to make physicians feel comfortable that those patients who have an unknown source of infection can be safely treated.

But one of the most common causes of infection in the hospital for which empiric therapy is given is the one that you are considering which is primary bacteremia. So I think it is an important issue in terms of actually being able to speak to physicians about how they use the antibiotics in the hospital.

So I just wanted to emphasize what I think is the importance of the topic that you are

considering to clinicians and patients.

The other thing I would point out is that, and maybe Jan Patterson can actually correct me if I am wrong here, but there are a number of epidemiological studies mainly from the CDC which have indicated that approximately 80 percent of what we call primary bacteremia is probably catheter-related bacteremia which has not otherwise been documented. Although the data that support that are kind of indirect based, again, on epidemiologic deductive reasoning, I think it is a reasonable deduction and it does come from the CDC.

In terms of the issues around metastatic infections that you have been thinking about, and I think John Powers made this point, and the timing of metastatic infection, I think a lot of these patients who develop medication infections during the course of therapy probably had it at baseline or close to baseline.

I don't know how many of you have gotten CAT scans on patients with left-sided endocarditis, but I have. You find a lot of things in there that

you didn't suspect clinically and I am sure that a lot of that exists. The question, then, is can the therapy that you give over a period of time resolve those preexisting, probably, metastatic infections. I think that is one of the things that you get at in a trial like this.

Finally, I will point out that I don't know how long it has been since a sponsor has submitted for an indication for endocarditis, but I think it has been a long time. This pathway would be a way to encourage sponsors to get back into the business of endocarditis. I think, without something like this, it is going to be hard for that to happen. So I think that is another reason to seriously consider this sort of indication.

So I will stop. Thanks.

DR. LEGGETT: Any questions for Dr. Shlaes? Jan, did you have any comment about the CDC?

DR. PATTERSON: I would agree.

DR. LEGGETT: Thank you.

I would like to thank all the speakers who

spoke during this session which will now be closed. We will continue with discussion of issues in studying catheter-related bacteremia. Dr. Janice Pohlman.

Sorry; John?

DR. BRADLEY: Not to complicate things more but, as we talk about organisms causing bacteremia, I certainly agree with separating Staph aureus from Staph epi and focusing on catheter-related and infective endocarditis. However, in pediatrics, there are at least two other entities that involve the catheter. One has to do with a neutropenic child who has got horrible mucositis and gets fevers and presumably a transient bacteremia from rectal ulcerations, occasionally oral ulcerations, so the organisms in the bloodstream reflect both gut and oral flora.

Secondly, as the neonatologists get better at saving the smaller and smaller babies, there is a whole cohort of children with short-gut syndrome. As those children have their oral feedings increased, we see a fair amount of translocation of

gut flora. These kids all have catheters in for parenteral nutrition and, when they get fevers, you draw the blood cultures and it has got flora. Subsequently the catheters remain infected because they have been in for a while and, presumably, the organisms that they are bacteremia with stick to the catheter.

Then you have to deal with an infected catheter. Although the source is probably the gut, there is no identifiable source, no erosion that you can point out. So, as we simplify things, I also want to complicate things.

Thank you.

DR. LEGGETT: Thank you. Dr. Pohlman.

Issues in Studying Catheter-Related Bacteremia

DR. POHLMAN: I learned that there is a problem being the last speaker of the day and that, aside from sort of the post-prandial siesta, people have already stolen your thunder and your talk, so I will try not to be too repetitive. But I don't want to get too far off track.

(Slide.)

The focus of my presentation this afternoon is to revisit the existing catheter-related bloodstream guidance document.

(Slide.)

I am going to start off--I won't go through this whole slide but sort of why we got there. As we mentioned, the numbers are subject to all our estimating, our surveillance data estimations. Prospective studies have identified attributable mortality rates as high as 12 to 25 percent depending a little bit, primarily, on the pathogens that have been isolated in those studies.

Again, the main epidemiology that we are looking at are the Gram-positive organisms, coagulase-negative Staph and Staph aureus with the other organisms falling somewhere down the list dependent on the patient populations you are looking for.

There is, obviously, a paucity of randomized clinical-trial data in the study of CRBSI. I guess I would add when this guidance document was developed, it was in the face of

increasing antibiotic resistance and the institution of vancomycin utilization control strategies.

(Slide.)

In terms of going back to where we were in 1999 and sort of the discussion, the issues, obviously, are still there. As mentioned, we did--in the guidance document, there were clinical criteria that were established to sort of help guide us to prospectively identify a patient that might be at risk from a catheter-related bloodstream infection.

However, we recognized that there was lack of pathognomonic signs and symptoms of catheter-related blood-stream infections. The clinical criteria fever is nonspecific. There was one study that said that up to 80 to 90 percent of new fever in the ICU is not related to catheter-related blood-stream infection.

Catheter exit-site inflammation is not very sensitive. Perhaps 85, 90 percent of catheter-related infections in prospective studies

are not associated with any inflammation at the exit site.

I think it was recognized that this was a very complex undertaking, tremendous heterogeneity in terms of the patient population, whether patients were acutely or chronically ill. The catheter types; was it a tunneled catheter or a non-tunneled catheter. Were these catheters in place for short-term or long-term duration? Certainly, we recognize that there is a difference in virulence of causative pathogens.

(Slide.)

I think the bulk of discussion at the previous advisory committee revolved around these two issues. One was how do we go about establishing the diagnosis of a catheter-related blood-stream infection. In terms of employing microbiologic criteria to determine that the catheter is involved with the infection as opposed to a clinical diagnosis of exclusion, bacteremia in a patient with a catheter and no other focus of infection presuming a reasonable strategy depending

on the clinical presentation of the patient to rule out another focus.

Then another big topic of conversation was the use of microbiologic criteria to identify the catheters as the source of the blood-stream infection. I think there were a number of issues in terms of discussion, a little bit of thresholds for what these criteria ought to be. The literature, if you look at the literature, you can find a variety of thresholds that are used.

The problem is if you set your threshold for sensitivity too low, you are going to lose some specificity in the overall diagnosis.

(Slide.)

Some additional issues that didn't garner as much conversation but were recognized as potential pitfalls in the study were the inability to estimate the magnitude of the antimicrobial treatment effect versus just catheter removal for organisms of low virulence that colonize the skin.

We talked a little bit before about the ramifications of adjunctive catheter removal

post-randomization and initiation of therapy where, if an investigator should decide the catheter is not needed anymore and pull it, what we would look at in a clinical trial as a clinical failure because the catheter is coming out even though there might not have been an indication of failure.

The last topic was whether we use clinical or microbiologic endpoints to define treatment efficacy. By that, I mean test-of-cure blood cultures.

(Slide.)

We heard a little bit before, and I really was trying to be discrete in terms of identification although this information was presented publicly at a workshop in an April, 2004 joint FDA-IDSA-ISAP workshop on catheter-related blood-stream infections. We have seen this data earlier that, out of 200,630 patients that were screened for potential admission to this catheter-related blood-stream infection, 75, or 2.8 percent of the population, were ultimately enrolled in the trial.

The primary reasons that were outlined were that 30 percent of the patients did not meet the microbiologic criteria for diagnosis. It isn't clear to me whether or not it was the fact that--I gather that it was that the cultures were not obtained versus the culture results were not definitive by the microbiologic criteria laid out, although that wasn't totally understood. And 20 percent, with some overlap, with the other exclusion criteria were excluded on the basis of prior antimicrobial therapy.

(Slide.)

So I am just trying to garner--at the point when we were putting this together, we had that information that had been presented publicly. So I was trying to establish how easy or how difficult is it to enroll patients in the trial figuring that the number of patients that meet the microbiologic criteria for the definition of CRBSI might relate to the method of screening.

There was a published report of a Phase II trial for the treatment of CRBSI using an approved

drug where 23 out of 39 patients, or 59 percent, enrolled had evidence of Gram-positive bacteremia or infection.

Then, along with additional pharmaceutical-industry experience where 25 percent of patients identified by clinical criteria and/or local inflammation met minimal microbiologic criteria for the diagnosis of CRBSI. That would include a peripheral blood culture plus a catheter exudate or exit-site culture.

I probably stand a little corrected because I don't have specific screening data on the total population screened. So I apologize because those numbers may overrepresent the number of patients that were actually studied. But when I was going back and looking at diagnostic methods, when you look at prospective studies of patients with clinically suspected CRBSI--and this was primarily in the trials that were looking at differential time-to-positivity--they yielded approximately 10 to 15 percent of subjects with microbiologic evidence of catheter-related

blood-stream infection.

The 10 to 15 percent rate, however, the patient populations that were primarily studied in these were cancer patients with long-term catheters. Actually, the largest study, I think it was only 4 percent of their population had microbiologic criteria that fit catheter-related blood-stream infection.

(Slide.)

So what has happened since the advisory committee in 1999? We have had the guidelines for the management of intravascular catheter-related infections released, a joint effort by IDSA, American College of Critical Care Medicine and SHAE. However, they are evidence-based recommendations. The data to support the recommendations is based on small clinical trials and not randomized controlled clinical trials.

The problem with using these to somehow develop our guidance, the guidelines, the management guidelines, assume that you already have effective therapy. They are useful for clinical

practice but they are not designed to assess the efficacy of new antimicrobial therapies.

(Slide.)

Now, turning to the CRBSI microbiologic diagnostics, there are two pathways to go down. One is where the catheter is maintained and one is where the catheter is removed. Obviously, there are reasons to prefer the maintenance of the catheter, especially in patients in whom access is difficult.

Historically, quantitative blood cultures have been the study methodology that people used. However, this is very--there are not very many hospitals in the United States or, I would believe, worldwide that do this. It is very labor-intensive. I think the number at the last advisory committee was perhaps 5 percent of hospitals are doing quantitative blood cultures.

The buzzword at the last meeting was this differential time-to-positivity which relied on automated blood-culture systems that--basically, blood that was collected through the catheter

became positive two hours or more prior to the peripheral blood culture.

Some other additional investigational techniques, looking through the literature, an acridine orange leukocyte cytospin which, actually, takes a little sample of blood from the catheter, you spin it down and you stain it looking for bacteremia DNA. This method actually was used, I believe, to stain catheters in the past, whole catheters.

There is also an endoluminal brush technique where you kind of go down the lumen of the catheter and then you culture the brush that you have used. However, I would say that those are pretty investigational. Stick to differential time-to-positivity.

(Slide.)

At the last advisory, there were two published studies that had indicated utility primarily in immunocompromised patients with long-term or tunneled catheters. A recently published study in the Annals of Internal Medicine

in 2004 indicated utility in patients with both short and long-term catheters.

However, when you look at the definition of short-term catheters, these were defined as catheters in place for less than 30 days. In terms of looking at the pathogenesis of catheter-related infections, we know that somewhere around up to ten days, the primary sites of colonization are the skin followed a little bit by the lumen in terms of direct contamination of the line. Long-term lines greater than 30 days, you have primarily intraluminal colonization so that somewhere in that window of 10 to 30 days, you have a switchover from the primary site of colonization.

One of the things that, when you look at these studies, and there were about six in the literature that I reviewed, the diagnosis of catheter-related bloodstream infection relies on some other previously studied methodology. There is not a gold standard. There is no quantitative gold standard. It looks at either in relation to semi-quantitative catheter tip or quantitative

blood cultures.

In terms of sort of what the results from this 2004 study, the sensitivity was lower in short-term catheters. Specificity was lower in long-term catheters. One of my problems when I read the literature related to this is that when you have concordant--obviously, you need concordant blood cultures, the catheter and the peripheral. But what happens is that, when people don't fit the mold, when they have discordant cultures, oftentimes, there isn't enough information published about the patients that don't have concordance.

I think sometimes there are some conclusions that are being reached that are a little bit of a stretch. But differential time-to-positivity, I think you need automated blood culture systems. You need some basic assumption on the process that those blood culture bottles are being inoculated evenly, that the processing time getting to the lab is the same.

I guess, additionally, in terms of is

there somebody there that can actually look at the bottle when the sensor goes off, is that really positive at that point in time or is that merely the sensor and the blood culture subsequently would not be positive at that point in time.

So I think there are some things to keep in mind.

(Slide.)

Problems associated with catheter-maintained diagnostics. If you can't aspirate blood back, you can't have a catheter culture. Which lumen of the catheter should be cultured? The sensitivity of cultures may vary, again, as I mentioned, establishing the appropriate threshold for positive results.

I think even in our current rendition of the guidance document, there is a catheter to peripheral ratio of 3:1 to 5:1. Which do we use? Problems associated in particular with quantitative blood cultures not available in many institutions. You can tell I didn't train or practice at an institution that had them because I think the

turnaround time is even longer than the 48 to 72 hours. It may be as much as 72 to 96 hours.

(Slide.)

So if you want to take the other tactic and you are going to remove the catheter, the primary methods are quantitative or semi-quantitative catheter-tip or catheter-segment cultures. The problems associated with these; oftentimes, the catheters are removed needlessly when there is really not a CRBSI. As with blood cultures, they take time so both of these are retrospective. You don't have the answer when you are initially screening patients when potentially you could randomize and treat.

Again, the establishment of appropriate threshold is the cutoff. Fifteen colonies is the appropriate cutoff, greater than 10

3. It depends on methodology. Some of them are organism-dependent. There has also been a study that demonstrated potential inhibitory effect of antimicrobial-impregnated catheters on subsequent catheter cultures. That is totally an in vitro

phenomenon but presumably if you had reasonably fresh antimicrobial-impregnated catheters and you don't include inhibitors in your media, you could actually inhibit catheter-culture growth.

(Slide.)

Then, in terms of the overall, do we really need this catheter-culture data? I think the general consensus of the 1999 advisory committee was yes, particularly when you are talking about an infection where the predominant pathogen is also the most frequent blood culture contaminant. If you are going to go down to using pulse-field gel electrophoresis to establish concordance, then probably yes, we should be looking at catheter data.

You could also take the contrary viewpoint that, if you have a patient with a catheter, you isolate coagulase-negative Staph from the blood, you have two independent blood cultures that have that result, no other obvious focus of infection, that is a catheter-related infection. So you could take that tactic.

We have seen alternative definitions proposed by the pharmaceutical industry. You see it in published studies, these categories of definite or probable or suspected catheter-related blood-stream infections in which patients with a catheter have a positive peripheral blood culture, hopefully, a second positive independent blood culture for organisms associated with skin contamination, there is no other secondary source of infection identified and the catheter cultures have either not been done--the catheter was pulled and you don't have that as a source--or there is no differential that is demonstrated.

(Slide.)

Then what I thought I would do before we try to consider where we are going to go from here is just kind of run through what the current guidance document says. The microbiologic criteria for diagnosis and, while I say these are criteria for diagnosis, they are actually included in the guidance document as inclusion criteria. We know we are not going to have these results at the time

that the patient is--or it is not likely that we are going to have these results at the time that the patient is randomized and therapy is initiated.

But the requirement is for concordant growth of the same organism from peripheral blood in one of the following; quantitative catheter blood culture, catheter peripheral ratio of 3:1 to 5:1, quantitative catheter segment greater than or equal to 10 3 colony-forming units or semiquantitative catheter segment greater than 5 colony-forming units regardless of pathogen, culture of the inner catheter hub greater than or equal to 10 3 colony-forming units for skin colonizers, any growth for other pathogens, culture of catheter entry-site exudate regardless of pathogen, and culture of infusate regardless of pathogen.

(Slide.)

Concordance requires that you have growth of the same species with the same antibiogram and, as I mentioned, pulse-field gel electrophoresis is strongly recommended for skin colonizers. When one

considers populations for analysis, the modified intent-to-treat population is defined by all randomized to meet the clinical and microbiologic inclusion criteria. That serves as the co-primary population for noninferiority efficacy analysis.

Outcome of cure is defined as resolution of entry signs and symptoms and negative blood cultures at test-of-cure visit.

(Slide.)

Now what I would like to do--this is a little bit separate from the questions but it is probably considerations based on the discussion we had this morning in terms of willingness to proceed or to go down the path of a primary bacteremia due to Staph aureus.

I think the options that we have at hand, one is to maintain the current guidance. The pros for this: there is a systematic approach to study of treatment efficacy; it maintains a current level of diagnostic specificity; it is not organism-specific and may provide data on catheter-related blood-stream infections due to a

variety of organisms.

I think the cons--we have already heard what the cons are in terms of difficult enrollment. It is hard to find the patients to actually fit these criteria to enroll in the studies; adjunctive catheter removal after randomization and initiation of therapy is problematic; antimicrobial treatment effect and infections due to low virulence pathogens is not known; and a single positive peripheral blood culture with a catheter-site culture raises issue regarding specificity of diagnosis, particularly for low-virulence organisms that colonize the skin.

(Slide.)

I guess if we maintain the current guidance, I would kind of like to get some feeling on whether the committee has any advice or suggestions for facilitation of clinical trials, what types of investigators, what types of centers, do you have a colleague that you want to volunteer or volunteer to be a principal investigator for some of these studies.

(Slide.)

The second option would be a modification of the guidance. In putting the word "major" here, it is perhaps a value judgment that I didn't want to put out there, but this would be sort of changing a definition. Eliminating the need for microbiologic criteria for the catheter-related infection would allow us to increase the number of patients eligible for inclusion and evaluability. However, it might decrease the specificity of diagnosis thereby decreasing the scientific rigor of the study.

(Slide.)

Perhaps third, and we touched on it briefly this morning, in terms of considering a catheter-related blood culture infection within the context of a primary bacteremia due to Staph aureus indication. I think the pros, in terms of this, would be that we are studying a virulent pathogen where antimicrobial treatment effect is better defined. Catheters are more likely to be removed.

In terms of this last pro that is listed,

you can actually look at the flip side of that and see a con in it, but it may increase the available population for study, although I think we have kind of talked ourselves out of doing the primary bacteremia Staph aureus indication. It would limit the patients that had catheters but it would have opened it up to patients with Staph aureus.

In terms of the cons of doing this, it limits the variety of organisms we study. There are certainly catheter-related blood-stream infections that are secondary to coag-negative Staph.

I think that, perhaps, there is still a lack of consensus on duration of treatment for uncomplicated cases. Does everybody treat for two weeks or do people choose to treat for four for uncomplicated cases? And then the problem of differentiating uncomplicated cases that become complicated on the basis of persistent fever or persistently positive blood cultures from early treatment failure in a drug-efficacy trial and need for additional diagnostic tests such as echo which

certainly add cost to the study.

I think, at that point, that concludes my formal remarks. If anyone has any particular questions?

Questions from Committee

DR. LEGGETT: Don?

DR. PORETZ: I just have a basic question. You say catheter, catheters. Are all catheters made of the same material? I mean, we are talking about it as if it is one thing.

DR. POHLMAN: No.

DR. PORETZ: Does that need to be broken down as to the type of catheters, the material it is made of, whether it is coated or not coated with antimicrobics?

DR. POHLMAN: You know, that is a good question. The studies that have been done have examined--there are different catheter types. There is, perhaps, greater association of infections or biofilm formation associated with certain types of catheters. Oftentimes, I don't think practitioners know whether or not

antimicrobial catheters are being used--you know, maybe whatever your supplier purchases.

So, in terms of for studies, for companies that are going out, if you are not in control of that, a variety of things could be happening.

DR. PORETZ: The data on the antimicrobic coated catheters seems to be pretty good. I mean, how popular are they at the present time? Are they selling? Are they being used commonly?

DR. POHLMAN: I don't think I can answer that.

DR. LEGGETT: John?

DR. POWERS: Last summer there was a meeting of the Medical Device Related Infections Group which is a group of investigators that wants to study this. I think one of their major complaints--this was in San Antonio last August. One of their major complaints was that these things were not being used as widely as they should be.

We analyzed some of that data and their effectiveness is highly dependent upon how you defined a blood-stream infection. The way that

blood-stream infections were defined in those was a positive blood culture plus a positive catheter tip associated with it. When you look at all blood-culture positivity, there is not much difference.

Then a couple of people wrote back letters to the editor with these trials saying, well, wait a minute. If you culture the cath tip and there are antibiotics on the cath tip, that is going to make the cath tip look negative. So the question is should you be looking, defining blood-stream infections as positive blood culture plus a cath tip because that is going to falsely look low in the people that have coated catheters.

DR. LEGGETT: Jan?

DR. PATTERSON: I just wanted to comment that in the infection-control community, they are not widely used primarily due to expense reasons. The antiseptic coated catheters, the chlorhexadine-coated catheters which are intermediate between non-coated and the antibiotic coated in terms of lowering risk for blood-stream

infection are more commonly used.

DR. LEGGETT: I think it also depends on where you start. It might make sense if your catheter infection rates were very high. Ours at our hospital are so low that they couldn't possibly be any better.

Thank you, Dr. Pohlman.

Questions to the Committee and Discussion

DR. POHLMAN: Did you want me to run through the questions here again?

DR. LEGGETT: Yes; shall we attack the questions there and then come back--okay.

DR. POHLMAN: In terms of ending my talk, I think I have presented the options as sort of maintain, modify the guidance or study within the context of a primary bacteremia due to Staph aureus.

In the interest of sort of continuing on from the morning discussion, what I am going to do is run through all the questions. I believe, two of the questions on this sheet dealt with catheter-related issues. But just to sort of

remind us and refresh our memories where we were, I have been told to proceed on through the questions.

No. 1 we did talk about extensively this morning, about the primary bacteremia due to Staph aureus as an indication, itself. What patient populations with Staph aureus bacteremia should be included in a clinical development program? Should bacterial endocarditis due to Staph aureus be a separate indication? If so, what additional information from clinical trials in serious Staph aureus infections should be available to support such a claim?

In terms of the catheter-related blood-stream-infection questions; should catheter-related blood-stream infections have its own indication or should this indication be subsumed into a more general primary bacteremia due to Staph aureus indication?

If it is a separate indication, what additional information on the treatment of serious Staph aureus infection should be available to support it? Can data on catheter-related

infections with or without bacteremia be included as a subset of the complicated skin-infection indication? What specificity of diagnosis would be recommended especially regarding common skin organisms?

And then the final two questions. Given that blood-stream infections due to Staph aureus have the potential to cause serious morbidity and mortality, what types of preclinical and early clinical information should be available prior to initiating large clinical trials? How many positive blood cultures are required prior to study entry in clinical trials of primary bacteremia due to Staph aureus?

Question 8; I don't know. Should I read through this, John? Okay. For the interest of completion; screening patients for admission into clinical trials is complicated due to factors such as the potential for an occult primary source of infection. What advice can you provide regarding a general approach to screening patients? Should patients with an identified focus be entered or

remain in trials? Is endocarditis a special case in this regard?

DR. LEGGETT: Should we address them in order to discuss? Is that what you guys would like? Okay.

Could we have somebody put the first question up on the screen so we could--the question is, should primary bacteremia due to Staph aureus be an indication? If so, what results from our other clinical trials would, in general, be expected prior to proceeding with clinical trials?

This morning, I don't think we completely wrapped ourselves around that. And with the comments of the Open Public Hearing speaker, Dr. Shlaes, I would like to have another little go at that and then, also, talk about what other clinical trials might take on the use of bacteremia for empiric therapy goes back to the point you don't know that that drug that stays very well in the bloodstream is going to go out of the bloodstream anyplace else.

So, without other trials showing efficacy

in other tissues, I don't know that that helps me very much to make that decision about using empiric therapy. I am sure I am going to get some debate about that.

Yes, sir?

DR. MALDONADO: Just a quick question. How do you define primary bacteremia because, in the morning, I sensed that there was not a very good working definition of what primary bacteremia--I mean, the words "primary bacteremia," people might think that is a blood culture that is positive. But I think that, in one of your slides, John, you attempted to actually define it with some other clinical caveats and that might actually help us to find out what the answer might be.

DR. POWERS: We had some internal discussion about what we should call this. One of the issues that came up was based on that the committee, in the past, had told us that bacteremia is not a disease. The question was do you call it sepsis? What do you call it?

We are open to any suggestions you folks

might have but the reason we were hesitant to call it bacteremia is that, technically, that just means a positive blood culture and we had to link it to some clinical signs and symptoms in the patient. That is why, when I put up that definition, that was in there of clinical signs and symptoms that go along with it.

But you are right. It implies just the positive blood culture.

DR. LEGGETT: Don?

DR. PORETZ: But, surely, you have seen enough patients in an emergency room to look at and say, this patient is sick. This patient may be bacteremic. They are having shaking chills. They are febrile. They have a high white count and your best medical opinion is you need to get them on an antimicrobic.

So you go over them and you examine them and their lungs are clear and their chest X-ray is negative and there is no pneumonia. And you get a urinalysis and the urine doesn't show any white cells or no evidence of infection. And their belly

exam is completely normal. So it is probably not an intra-abdominal process but yet you are really worried about them.

They have no skin infection. You are worried about them saying they are really sick, and I need to put this person on an antibiotic. The white count is 20,000. That is a clinical decision you make. I am not sure it is that hard, really. So there are people who will come in and you say the patient is sick and the patient looks like they could be bacteremic. We find no other cause. We are going to put them on an antimicrobic anyway. You are going to draw blood cultures anyway; right?

Yes, it may turn out that the following day they will blossom into a pulmonary infiltrate or something else will happen but, nevertheless, I think that is a valid clinical decision at that time.

DR. POWERS: I think there is an issue of what Sam was bringing up. There is the other end of that spectrum, similar to what Jim said. Bacteremia, if you just look at the word, could

also mean the guy that had one blood culture for Staph epi that pops us six days into the time he is sitting there and you walk into the room and he is reading the newspaper and he looks fine.

That is what we don't want in bacteremia drugs.

DR. PORETZ: But that is not the person we just described who you are examining?

DR. POWERS: Right; exactly.

DR. PORETZ: So you don't include that in your definition.

DR. POWERS: Right. Sam's issue was bacteremia as a definition.

Let me bring up another, though, and that is that the FDA doesn't really have empirical therapy indications except in one spot and that is febrile neutropenic patients because what we want to know in clinical trials is exactly what Jim just said. We want to know that the drug works in a defined disease.

The fact that you choose it to use it for empiric therapy is because you know it is going to

work in that particular setting if the patient, in fact, turns out to have the disease you think they might have. But, in terms of studying it, one of the biggest issues, when I showed those two big circles on the graph, was actually picking out, first and foremost, in a clinical trial who has the illness you are trying to study.

So we probably don't want to go down the path of designing an empirical therapy kind of study in this indication.

DR. LEGGETT: Janice?

DR. SORETH: I am trying to remember what I was going to say. Oh; I know. I think, to come back to Dr. Poretz' point, as well as Sam's, I think that we probably all readily agree on what patients look like and what they are labs look like and their studies look like when they endocarditis and they have Staph aureus in their blood, and that labeling drugs for that patient population makes sense.

We have done it in the past and we really would like to do it again. So we are happy that

there is some ongoing inquiry in this arena in endocarditis.

That said, to come back to the patient you described, again, like pornography, God, I know it when I see it. We are just trying to agree, if we can, in the setting of a clinical trial, what the appropriate inclusion/exclusion criteria would be for those patients and that, if we can agree on that, it would seem to me, then, to make sense to so label a drug study that had an appropriate risk/benefit ratio for you and all the other physicians who are faced with that person in the E.R., on the ward at 3:00 a.m., in the boondocks, et cetera, because it would seem, perhaps, that that would merit labeling, perhaps in a package insert. If not, then that is why we are here today to talk about why not.

DR. LEGGETT: Jan?

DR. PATTERSON: Well, I would agree with the definition of primary bacteremia that is on Slides 3 and 4 of Dr. Powers and that is the signs and symptoms of infection with positive blood

culture for Staph aureus, no identified source at the time of enrollment and then, on Slide 4, saying bacteremia related to an intravascular catheter, often a diagnosis of exclusion so it may be logical to include in this category.

With diagnosis of exclusion, I think that a physical exam, an echocardiogram, preferably a TEE, a chest X-ray and probably a C.T. abdomen preferably with contrast would be the screens I would use to exclude other sources.

But I would feel very comfortable including catheter-related bacteremia in that definition of primary bacteremia of Staph aureus. I think that it is logical to differentiate it from coag-negative Staph because it is very different than that. It is much more of an acute and invasive disease and it is more important disease. It is becoming more and more common and I think that leading to a possible indication of endocarditis is important because we are seeing more endocarditis.

We don't know that we have an ideal

treatment right now and there are more drugs to treat it so what should be use. I think that is really an unanswered question.

DR. LEGGETT: My two bits and then give it to Alan about primary bacteremia. One of my colleagues, not to say my boss, is a stickler for using erysipelas when you are talking about a Group A streptococcal infection and everybody else in the world calls it cellulitis. The problem with the primary bacteremia is that we all know what we are talking about. It is the pornography issue.

So I don't know that I would be so hung up about using something that all clinicians understand. But you have got other issues. I understand about that.

Alan?

DR. CROSS: I just wanted to reemphasize the obvious. Although this first question is talking about primary bacteremia due to Staph aureus, sometimes our discussions here were lapsing into Staph epi or coag-negative. They are quite distinct entities. I think we have to really bear

this in mind.

But, John, in your excellent review, did you happen to find out--how often does Staph aureus bacteremia occur in the absence of fever, white count or any other clinical symptoms? I am sure it occurs but do we have any handle on that?

DR. POWERS: All we know is looking at endocarditis studies in the past, the number that gets quoted in those is 5 percent. So it is not impossible for it to occur, but it doesn't--but then, again, I think it is what Dr. Poretz brought up, you don't go looking for it unless the patient has those signs and symptoms to start with. So it becomes very circular reasoning.

DR. CROSS: But the point is we are not going to have a person sitting in bed reading a newspaper with a Staph aureus bacteremia unless they--

DR. POWERS: And I think that gets back to what Dr. Patterson said about that, but that can happen with Staph epidermidis. The question is separating those out.

DR. LEGGETT: Nate?

DR. THEILMAN: I was wondering if we could ask Barth Reller to comment on that because he did a very large study of blood cultures in the 1990s, I believe, and characterized all bacteremias with regard to their significance. Correct, Barth?

DR. RELLER: To comment and, in part, address that and follow up on Don's comments. One of the difficulties I think we have in grappling with these terms that have been used is yes, for an experienced clinician, it is straightforward of what to do. But that is different from what the requirements are for infection-control practitioners in categorization for nationwide survival for NIS which, I believe, and Jan, correct me, if that is not where the concept of primary and secondary bacteremia are embedded in the literature and practice.

So it was done for NIS to capture those persons who have an identifiable focus and the bacteremia is perceived to be a consequence of that versus primary bacteremia. The reality is, with

the primary bacteremias in that definition, with coagulase-negative staphylococcus, we know that there is a lot of noise because, when Jerry Tocars looked that, maybe 30 percent, maybe more, of the ones in that definition, a single positive blood culture for coag-negative Staph and intent-to-treat which no one here would accept for entry into a clinical trial.

Now, the point of this is that for epidemiological purposes, at least 80, maybe 90, percent, maybe 95 percent, of primary bacteremias with coagulase-negative staphylococci are, in fact, catheter-associated.

With the other bacteremias that the committee, in past deliberations, have shied away from, this idea of spontaneous--everything has a source. I think the field has evolved so that one has pneumonia where bacteremia may be present and adds great specificity so you have pneumococcal pneumonia or lower-respiratory-tract infections, pneumococcal pneumonia accompanied by bacteremia or you have complicated urinary-tract infection

accompanied by E. coli bacteremia.

So the labeling may be including bacteremias. So it is approved for complicated urinary-tract. It is approved for lower-respiratory-tract infections, community-associated pneumonia, including those that have bacteremia with pneumococcus.

The problem with Staph aureus bacteremia is, in Don's patient, if he identified a focus, it would be a priori a secondary bacteremia. Easy. But the reality is, I think, that most, or a very good share, and an increasing share, of staphylococcal bacteremias, especially those that are healthcare associated, whether coming into the hospital from chronic dialysis, et cetera, there is not a necessarily confirmed source so that one has a disproportionate number of what would be, for epidemiological purposes, classified as primary bacteremia and many of those are associated, either chicken or egg, with catheters.

The studies more recently increasingly show that, especially healthcare-associated and

especially those with diabetes and long-term catheters and tunneled catheters, that, although it may have started with the catheter, a break in the skin and get in through the catheter, that there are a lot more complications associated with that including that most staphylococcal endocarditis now is not Nolan and Beaty 1976 community-associated but most staphylococcal endocarditises are hospital-acquired and they are associated with the catheters and the need to separate out that.

So I think that one of the difficulties on this coming to agreement that there really is agreement of the uncomplicated staphylococcal bacteremias is the constraints of the past of the definitions for NIS and the concepts of bacteremia as a complication of a primary source of infection, and the two in a very complex way, intersect here. The ones that are straightforward, that get the shorter course of therapy and are readily recognized and the ones that, boy, depending on how you search, the horse may already be out of the barn and they will come back to bite you if you

don't recognize those and if you give short-course therapy you are going to be sorry.

To me, I know it is a long comment, but I think that is part of the reason that it is difficult, even though there is agreement, to get a handle on what is the definition for the purpose of enrollment in a clinical trial that is doable.

DR. LEGGETT: Any ideas?

Don?

DR. PORETZ: Just a matter of semantics. We are looking for sources of the infection. Consider the use of the term "entry site." Maybe it was just a break in the integrity of the integument of the skin or a mucous membrane. That could have been the entry site.

I don't think it has to be a source of infection. It doesn't have to be an abscess or a cellulitis. So maybe consider the term "entry site."

DR. LEGGETT: Or what we always say, "portal of entry."

Barth.

DR. RELLER: I think others should speak first. But I won't forget.

DR. LEGGETT: Okay.

Sam?

DR. MALDONADO: John, I know that empiric therapy has actually worked well apparently regulatoryally for patients with fever and neutropenia and also clinically. The reason I said that, I mean, when you, as a clinician, see a patient, you don't treat, really, a bacteremic patient with Staph aureus. You treat a patient, period.

You treat a clinical presentation. That doesn't mean that you will disregard, when you are looking at your endpoints, the microbiology. But if that clinical presentation is well defined, even regulatoryally defined, what kind of patient you are trying to capture. For example, a patient who has a systemic inflammatory response syndrome and you can define it, whatever, if you think that some of those definitions are not independent. There are ways to lump them, for example; for example,

hypothermic tachycardia/tachypnea, either of those, and leukopenia or leukocytosis.

So that is a clinical presentation that actually, as Dr. Poretz said, that is what you see when you get a patient and that is what makes you, as a clinician, treat the patient.

Why wouldn't it work, if it has worked regulatoryally and clinically with immunosuppressed patients, in patients who are not immunosuppressed.

DR. POWERS: I think it is way too broad to say that there haven't been regulatory issues with empirical-therapy trials in the febrile neutropenic population first and foremost of which if you even take something like antifungal therapy, we have no idea what the benefit of amphotericin B over placebo is.

We made a decision in 1995 that we were going to set that margin at 10 percent but we had a meeting at the Bacterial Mycosis Study Group last year about all these issues regarding empirical therapy. It has not been easy, including a five-component composite endpoint that we have

heard all sorts of comments about.

So, to just sort of say that that is easily regulatoryally done, I don't think that that is actually the case.

The other issue is what Dr. Reller was bringing up earlier about the reason we divide these indications into specific body sites is because each of those has a different natural history and a different progression and things that happen. We know that when a person shows up in the emergency room, I mean, it is not just that clinical presentation. What you are doing is doing a good history and physical trying to find out where the portal of entry might be or at least try to come up with that best guess.

So what we are trying to say is to differentiate between management of patients and determining the efficacy of a new drug. It is fine that you decide to manage your patient by empirically giving the drug but you do that because you know that drug is already effective for treating those various diseases that you are

worried about. That is a different setting than actually trying to determine whether a drug is effective or not in an experimental setting.

DR. LEGGETT: Jan?

DR. PATTERSON: I think one of the things we were asked to address is what would make it easier to do these studies and still have good scientific data.

I think one of the things we have been talking about, and I agree with, is that we could extend the time on antibiotics to 48 hours for Staph aureus. I think there is not going to be a difference in outcome between 24 and 48 hours of therapy. So that is one thing we could do.

Then I was intrigued with Dr. Powers' comment about not using the positive blood cultures in the lab to screen but starting it empirically. I think the problem with that is then--for instance, one of these studies, 30 percent of the people that were excluded it was because they lacked microbiologic data.

So you wait for the positive blood culture

and allow a little more time on antibiotics or you have more people that you screen that don't get to stay in the study. So it is kind of a balance. But I think if we did allow more time on antibiotics, particularly 48 hours, that that would help some.

DR. LEGGETT: There is no free lunch. You either enrich your population or you dilute it and there is a problem either way.

Don?

DR. PORETZ: But I have been at the other end trying to get patients on protocols. It is very, very frustrating and very difficult. You can't get the patient on a protocol because it is too late or the culture--all those things that have been mentioned. I think, for pharmaceutical companies who want to do these studies, it makes sense.

You may end up putting more people on at the time the patient is originally seen, and many of those people may not be evaluable. But accept that as a fact. I think you will get more results

than you will at the other end by restricting the number of people you can put on a protocol.

DR. LEGGETT: Alan?

DR. CROSS: I would like to emphasize that. I mean, actually a point they made this morning is to just start people right at the outset and, at that point, enroll them in the trial and prospectively define how you will handle endocarditis and perhaps other complications.

I think that probably, Tom, it is worthwhile mentioning a discussion was had after that. Tom brought up the very valid point of what happens, for example, with certain biologics for sepsis when lots of people were enrolled on the agent and then prospectively analyzed only those Gram-positive bacteremia.

Tom made the important point that, when you do that kind of study--that is, enroll lots of people but prospectively define a subpopulation--that you still have to follow all those you enrolled who didn't qualify with your Staph aureus bacteremia. You still have to follow

them in terms of outcome and safety.

But I think that is doable. I would rather capture patients up front seeing how difficult--and I have had the exact same experience that Don has had.

Lastly, I still wonder about just the operational point which I think still has some validity about Staph aureus bacteremia due to "a removable and non-removable focus." That is something that most people understand and there already is at least some paradigm about how you might treat those two patient populations differently.

DR. LEGGETT: Joan?

DR. HILTON: I would like to come back to some study-design issues and to return to your statement earlier about the purpose of performing clinical investigations is to distinguish the effects of a drug from other influences such as spontaneous change in the course of the disease.

What I picked up on there was change in the course of the disease. I think, when we use a

cross-sectional study design, we assume that all the patients are similar at the starting point. I think that is not what we have got here.

To address that, I have a couple of different proposals. One is to use a longitudinal outcome. One possibility is time-to-treatment-failure but I think something that would be a lot more sensitive would be some type of a continuous response. Maybe the one that Janice suggested, differential-time-to-positivity, or some others, could be put on the table. But anything that captures the patient's status at baseline would be a lot more sensitive to use.

To address the heterogeneity in the pool of patients and this issue about baseline, the duration of the baseline period during which you collect data and characterize those patients, we want to know who the responders are. We need a lot of baseline data in order to characterize who responds and who doesn't.

Ideally, that is all collected prior to randomization. But if it is collected on a very

strict per-protocol basis, it could still be collected for some window of time post-randomization and still be used as a covariate in the analysis. So a couple of possible variables I was thinking of.

Another one is whether or not the device is removed during the study follow-up period. There is an example, not of a baseline sort of covariate but as a time-dependent covariate. So, again, if you have got a longitudinal outcome variable, you can analyze a time-dependent covariate. So I think there are a lot of reasons to be a little more flexible with the study design and use some of these.

DR. LEGGETT: John?

DR. POWERS: I think we have thought about some of the issues of looking at longitudinal outcomes and actually adjusting for some of those things that occur post-randomization. We have talked a little about that internally. It depends what outcome you are going to look at longitudinally or if we are going to use--you are

suggesting, like, time-to-analysis?

DR. HILTON: I think that is one possibility but I prefer, myself, some sort of a continuous repeated-measures variable.

DR. POWERS: Because we looked at--if you take something like this that has a high mortality, whether you die on Tuesday or die on Thursday doesn't seem very clinically relevant. So, depending upon which outcome you are following over time, it may be either useful or not useful. Time-to-death probably doesn't make any sense. Time-to analyses have been used in HIV trials; time-to-loss-of-virologic-response, but that is a chronic ongoing illness. Time-to-death here probably doesn't make a whole lot of sense.

DR. LEGGETT: Did you want to add something, Janice?

DR. SORETH: I was just chuckling at John's pronouncement that it didn't matter whether you died on Tuesday and Thursday. It probably did to the patient who died, but that is neither here nor there.

DR. LEGGETT: John and then Chris.

DR. BRADLEY: The whole concept of primary bacteremia is something that we are trying to both acknowledge that there is a clinical definition and define for a study. From old data, it is clear that we all actually have intermittent bacteremia all the time, so a primary bacteremia with no focus is not unusual.

For the patients that end up, whether they are children or adults that end up coming to medical care, they probably have other factors that are involved in a persisting continuing bacteremia even if there is no particular focus. In many of the kids that we see with osteomyelitis, you may find a skin lesion, a portal of entry, which isn't an abscess, doesn't look like something that you would even give a second thought to ordinarily, but when you examine a child who has got osteomyelitis for their entry site, more often than not, you can find it.

So, whether we define primary bacteremia as bacteremia with no focus and whether you are

including the skin as the focus or not, I think, is just semantics. If you exclude skin, if you say, sure, you can have an entry site but it is not considered a focus of infection, I would be happy to consider that primary bacteremia.

Likewise, if there is a gut focus from these kids with short-gut syndrome, I would agree to define that as primary bacteremia even though you can probably define where the organisms are coming from. It is how we define it for the study.

In terms of enriching for those patients who look like they are septic and are more likely to have bacteremia, I think the sicker you are on the spectrum, the more likely you are to have actual bacterial infection. With pneumococcus, this was beautifully demonstrated in children. So, in designing a study, we can either go with making them febrile, have systemic inflammatory response with shock and have very few enrolled but, of those enrolled, many will actually be bacteremic versus saying, well, anyone with fever and an elevated white count can go in, in which case, you will be

enrolling many who don't have bacteremia. It will be a more sensitive test but the specificity and how easy it is to actually evaluate their outcomes would be much more difficult.

I would favor enrolling the more severe patients. The one that you described would be the one that I am particularly interested in capturing and seeing if a drug works.

DR. LEGGETT: Chris?

DR. OHL: Since I put my hand up, I think a lot of the comments have been addressed. One word of caution. I think we need to be careful and I am probably stating this for the record more than anything, but going down a slope of going towards empiric treatment of sick people with antibiotics, we have got to be careful. I don't think that is really the intention of this. But I just want to make sure that is on the record.

We are going to need to continue to have to have definable infectious disease states at some point or another. Then I am very happy to hear Alan's comments straight after that, and I am not

going to repeat them all, but I think that there may be some meat in there that might be helpful as long as the clinical trials can be designed to fruition so that we don't end up repeating the same thing with catheter infections where we have to enroll an inordinate number of people. There may be some ways to do that and maybe now is not the time to discuss all those.

I think, within this purview, including catheters in that discussion is genuine and can be done because it is the clinical reality that is a good amount of them. I think Jan's ideas of a reasonable number of studies up front to rule out those primary infections that we would reasonably look for as clinicians in the first few hours of infection is also reasonable.

DR. LEGGETT: Tom and then we can decide whether we want to take a break or keep pressing forward.

DR. FLEMING: I would like to revisit a couple of the issues that we have talked about here. One relates to how can we allow for easier

enrollment into these trials so that they are more achievable. If we need, for example, 300 patients to evaluate treatment effects or 300 per arm, whichever it turns out to be, if we are modifying the enrollment criteria in ways that increase the number of people who we have in our analysis, then that is, in fact, a step ahead.

So if we are saying, for example, that we are going to allow 48 hours of anti-Staph treatment rather than 24, such that we are substantially increasing the number who are eligible and will be retained in the analysis, if we believe that we haven't diluted the focus of our assessment, we will, in fact, have gained substantial efficiency. I think that is very rational.

On the other hand, if we allow for easier enrollment of people who we are expecting, in all likelihood, to, in large fraction, be excluded based on subsequent assessments that are made, then we are not coming up with any net increase in efficiency and I think we are actually complicated the analysis for reasons that Alan was referring

to, that if you, in fact, end up enrolling 600 people but only analyze 300 because, retrospectively, only 300 are really, in fact, meeting the eligibility criteria that you are interested in, you are technically now not coming out ahead.

You still only have 300 but you have complicated the analysis because you now have 600 people that you have treated and you have to, in fact, assess the safety profile on all 600 which was, in fact, part of what led to problems in severe sepsis with agents that were targeting Gram-negative sepsis when they, in fact, were enrolling large numbers of people who ultimately were not eligible.

So I would suggest that what we focus on here is ways of increasing the numbers of people who would actually be included in the final analysis. That will be, in fact, allowing us to make these studies more achievable.

And then the other point; I would like to support a couple of issues that I think I heard

from Dr. Hilton. One is that it certainly is to our advantage for us to be able, within what is practically achievable, to get as much baseline information as we can that will allow us to have a more efficient analysis based on our ability to define what are the characteristics of people at baseline that, in fact, might be predictive of outcome or effect modifiers.

I also agree that, for the outcome measure, it would be important to try to capture what is really globally important here. So, rather than just focus on the blood cultures, certainly focus on signs and symptoms but also, I believe, the really critical elements of what happens post-randomization for metastatic infections and time-to-death and I.E.

I do endorse what Dr. Powers was saying, though, about when you do use that global information, how do you do it? Do you use it as time-to-event or do you use it in some analysis method that takes into account all of the information but for death, for example, if it

occurs, does it matter if it occurred at Week 1 versus at Week 2. So if, in the end, that Week 2 mortality is 30 percent but we have improved mortality by 5 percent at Week 1, but there is no improvement in mortality at Week 2, this is an acute setting and so time-to-event isn't in fact, particularly relevant there.

Where time-to-event is relevant is in a chronic setting. It is not just whether the event occurred but how soon it occurred mattered. So, if we are talking about a 30-day outcome here, I wouldn't consider time-to-event as being additively informative but I would consider the multiplicity of different components of the endpoint to be very important.

So if we just said success/failure, where failure is the occurrence of any one of the above, we might be losing information--than if we were taking into account, in a more global multivariate fashion, did the patient die, did the patient have metastatic infection, did the patient have I.E., did the patient have clearance of signs of

symptoms, did the patient have microbial clearance.

So there are ways that we can increase the efficiency by taking into account all of the relevant aspects although I think the time-to-event aspect isn't additively informative.

DR. LEGGETT: Barth. And then let's take a break. Go ahead and talk and then we will take a break.

DR. RELLER: I would like to float a potential way out of the box for consideration. First, I think we might make more progress in building on a complicated/uncomplicated paradigm because there is a good history in the trials and regulatory arena with those definitions and leave aside, for the moment, primary/secondary NIS because, particularly in the primary related to catheters, I think there is some reconsiderations going there on what constitutes a good database for those. First point.

The second is I think it would be easier to work with if we think of coag-negative and Staph aureus with two different approaches. I think what

has been done for catheter-related bloodstream infections already related to coagulase-negative are pretty close to the mark, maybe some tweaking but pretty close.

The reason for that is that almost all real coag-negative staphylococcal bacteremias, which is the minority of all of them, are device-related and, among the device-related, the most common, far and away, are catheter. I am aware of the lugdenensis, native-valve endocarditis or the lugdenensis like or--et cetera. But I think that would be easier to deal with.

Then, for the staphylococcal bacteremias, the way I am trying to put together everything that we heard today and from the past and the literature is I would conceptualize as complicated or uncomplicated. Okay; how do you define that?

Well, complicated to me is--or lets do uncomplicated first. Uncomplicated is with a specified search, the elements to be put in place, a doable, practical, financially feasible search that there is no source that is

pathophysiologically recognized to be associated with bacteremia. There is no osteomyelitis, et cetera.

Most of those are going to be associated with catheters so that what one would do there is to separate out those catheter-associated, or maybe catheter-initiated, that already have resulted in problems that are recognizable so that if you can't find any source and you have got a catheter, there is an uncomplicated.

Then the complicated ones would be ones where you do already have a complication, the pyogenic arthritis, the osteomyelitis, the splenisepsis and including those with endocarditis. So a key point in the complicated ones is endocarditis yes/no because one could have osteomyelitis and endocarditis or septic joint and endocarditis and then the endocarditis yes/no has to do with the duration of therapy and the utility of TEE for management because in the endocarditis with Staph aureus, you have got the surgery/no-surgery aspect of it.

So I think that may be a framework in which to get specifics around it that is congruous with the past and clearly those patients who have complicated denoting a source, most of those are going to fall, if not all of them, into the secondary if you were looking at from an infection-control practitioner's perspective.

But I am thinking more in terms of clinical care, clinical-trials, perspective. So I think the epidemiological surveillance needs and the clinical-trial needs and the clinical-practice needs overlap like the Venn diagrams but they have their distinctive peculiarities that must be kept in mind in order to not get it into--we all agree that we can't define dilemma.

DR. LEGGETT: Let me see if I understand because if I do, everybody does. Uncomplicated would be whether or not you have a catheter but you can't already find a complication. Complicated would be, at the time of enrollment, you already have a complication.

DR. RELLER: Basically, that's it, and

including endocarditis at the get-go.

DR. LEGGETT: John?

DR. POWERS: We can ask this question after the break if you want.

DR. LEGGETT: Go ahead.

DR. POWERS: The question is that the issue that we came up against was those complications may occur within a short period of time. So, in other words, you get enrolled in the trial and--you get enrolled on a Friday afternoon, heaven forbid. Your echo isn't getting done. We all know that. And it gets done on Monday so you are three days into the trial and your echo is positive.

Now you have a complicated infection but you got enrolled in the uncomplicated trial. And then there is another one. Then the second thing is those complications are not all the same. How would we lump together osteomyelitis, septic pulmonary emboli, endocarditis all into that complicated?

DR. RELLER: I am trying to remember the

numbers that Frank Tally and others presented. Do I think infective endocarditis and osteomyelitis are different, and there are some different therapeutic and intervention considerations? Yes. But, I mean, if we divide them into all of that, then we are back to staphylococcal osteomyelitis with or without accompanying bacteremia.

So this was not the solution but a proposed approach to the solution. I mean, there has to be a degree of lumping even of things that are not exactly similar if you are ever going to have enough numbers to put them into a logical category.

One of the things that was driving my consideration on this is you either have the approach of, if it is staphylococcal bacteremia and it is real, everybody gets four to six weeks of therapy or that--whether it is endocarditis or osteomyelitis, it may mean four weeks of parenteral therapy or six weeks of parenteral therapy. But if it is none of those, et cetera--so it is--and I think the 48 hours is a good point.

The 48 hours, you know, may be too lenient for the uncomplicated but, for the complicated, I don't think what is given in the first 48 hours if the patient is still alive is really going to determine what the ultimate outcome is in those patients. It is going to be the drainages and the--you know, et cetera.

So it as an attempt--because, in the uncomplicated, many of them in adults especially are going to be associated with catheters, some in pediatrics. But that uncomplicated bacteremia with Staph aureus where no metastatic complications are delineated at the outset would encompass the kids with staphylococcal bacteremia with breaks in skin, the pimples, and the "I can't find with a reasonable effort."

DR. LEGGETT: Why don't we take a break and return to this. It is 3:15; 3:29. That way, by the time we sit you down, it will be 3:30.

(Break.)

DR. LEGGETT: We agree to disagree about No. 1 and move on to No. 2. We have got to get to

No. 8 by 4:30.

DR. FLEMING: 30 seconds, real quickly on two points. Having argued against time-to-event analysis for the death endpoint in this setting because the major signal is is there a difference in whether you do die or not die. It doesn't matter in a relative sense so much whether, if you are going to die, if you die at Day 3 or Day 6.

In contrast, as this committee had discussed in the past year in acute bacterial sinusitis, the same thing would be true in acute otitis media. In those settings where resolution is going to occur with almost 100 percent, the signal is in how soon resolution occurs, resolution of signs and symptoms.

So I wanted to make sure that the message wasn't being conveyed that time-to-event isn't ever useful. In those settings, it would be the right thing to do.

The other point that I had wanted to add to is, while I very much endorse the concept that it is important to get as much baseline information

as possible to allow us to address some of this heterogeneity and improve some of the precision in our estimate, my own sense is, if we are going to use information post-randomization, information such as catheter use post-randomization, we have got to be very confident that the intervention, itself, is not influencing that outcome because, if it is influencing that outcome, now are estimating--if we use time-dependent covariates, now we are factoring out part of the actual signal or treatment effect.

DR. LEGGETT: Question No. 2; what patient populations with Staph aureus bacteremia should be included in a clinical-development program. I mean, we have been talking about that the whole time we have been talking about No. 1. I think the last thing to say about that is we already, this morning, talked about, I think, our general feeling that we would like to see concurrent or previous clinical trials so that we know that the drug is going to be effective where the metastatic foci from bacteremia are going to end up.

Anybody else want to say anything about No. 2? Chris?

DR. OHL: I think that all our previous discussion encompasses this enough that I don't think any more discussion is warranted.

DR. LEGGETT: Janice?

DR. SORETH: Those specific other serious infections would be serious pneumonias--

DR. LEGGETT: Yes; pneumonia, even though that is going to be hard to do because there are not that many Staph aureus pneumonias that I know for sure are--osteo--

DR. SORETH: You are getting to the point where you have some, I think, ideally, prior knowledge of the penetration of that drug and how patients fare when they are on it with serious and life-threatening infections in general.

DR. LEGGETT: Right.

DR. SORETH: Which may include some experience, however limited, with Staph aureus.

DR. LEGGETT: And I think skin and soft-tissue is important and maybe osteo/arthritis

but certainly osteo would be nice.

DR. SORETH: Right. Tend not to get that one, but that is okay.

DR. LEGGETT: Yes; I know.

DR. SORETH: We will keep trying.

DR. LEGGETT: Jan and then Nate.

DR. PATTERSON: I just wanted to say that, in terms of patient populations, I would hope that the pediatric population would be studied because of this increasing problem of MRSA and also that we do see a fair amount of Staph pneumonia in terms of nosocomial pneumonia. Then, last year with the flu season, there were a number of cases of community MRSA pneumonia in children as well that were associated with bacteremias and very invasive type pneumonias.

DR. LEGGETT: Does that mean you are wishing to avian flu?

Nate?

DR. THEILMAN: Just to the issue of what patient populations we could liberalize our entry criteria for and addressing the issue specifically

of 48 hours of prior treatment being acceptable, well, I should just throw this out. What is the evidence for 48 hours or prior treatment with, say, vancomycin would be acceptable?

For instance, if 50 percent of the drug's success is achieved in the first 48 hours of treatment, and we study Drug X beginning at 48 hours and find it to be effective, we could be encountering some misleading data.

So I just wonder if additional studies might be needed at that point to look at initial clearing or other evidence for what really happens in those first 48 hours of therapy.

DR. LEGGETT: One point that hopefully we will bring up again in the animal models, I can tell you that you don't get any killing with vancomycin at all in a mouse thigh model. So I am not really too confident that that is going to happen in people.

Janice?

DR. SORETH: Also, if the vast majority of patients in a trial have multiple antibiotics for

48 hours, or whatever the period of time is, we usually include that information in product labeling. It is not to say that someone isn't free to use it however they please off-label or approximately according to the label, but at least we try to incorporate that information into the product insert so that physicians can see how close they are or how far off base they are in choosing to use it this way or that way.

DR. LEGGETT: Alan?

DR. CROSS: I think, just to reemphasize a point that Barth made before the break is that, if we are talking about complicated or non-removable infections, it would be unlikely that 48 hours of an antimicrobial would cure that.

DR. THEILMAN: In uncomplicated, it could be.

DR. PATTERSON: I think with Staph aureus, it doesn't.

DR. LEGGETT: Agreed. No. 3; should bacterial endocarditis due to Staph aureus be a separate indication? If so, what additional

information from clinical trials in a serious Staph aureus infection should be available to support such a claim.

Again, we go back over stuff we have been talking about but maybe we could make it a little more specific.

DR. MALDONADO: I am sure this question was prompted by something. Why is that definition of an indication so specific? Why the need to be so specific for Staph aureus?

DR. POWERS: I think what we were really getting at here is can we enroll patients who have Staph aureus bacteremia, get the echocardiogram and, if they have endocarditis, leave them on the drug and get some experience with endocarditis within these trials as opposed to making folks go out and do separate entire studies for endocarditis.

DR. LEGGETT: Since we know that we can't really predict who is going to get endocarditis and a major portion of folks who get Staph aureus bacteremia are at risk, I would not want to exclude

the very people that I am most worried about.

Additional trials in serious Staph aureus infections should be available?

Oh; sorry. Chris?

DR. OHL: Sorry; I was just going to make a comment and I forgot to raise my hand. This gets back to the comments I was making this morning. I think that, since such a large number of these patients, as we saw this morning from the early results of a trial, are going to have endocarditis. I think that information would be useful to have and I would say yes to that question.

DR. LEGGETT: In terms of what other clinical-trial data, I think the similar sorts of things as what we have been saying before.

No. 4; should catheter--oh; sorry Barth.

DR. RELLER: On No. 3, just so it is captured in the record, although alluded to earlier, I think, before a trial would be allowed to retain patients who have endocarditis, as opposed to being dropped out, that there must be sufficient evidence of efficacy of drug against

Staph aureus in other sites. It may be skin and skin-structure infections. I don't want to get into the specifics, but I mean there should be a sufficient body of an data, other site infections, to say that this is an ethical thing to do, to keep the patient on a drug.

I am in total agreement that if it seems reasonable and there is a reasonable basis that it would be good to include because that is really the acid test for complicated--I mean, if it works for endocarditis, it will work for--assuming there is penetration, unless there is something special about getting into bone, but for most things, if it works for endocarditis, it will work for other complicated staphylococcal infections with the appropriate drainages and other things.

DR. LEGGETT: John?

DR. BRADLEY: I think the issue can be more complicated than that given the fact that many of the drugs that should be active in endocarditis would not be active against metastatic infections like in the CNS or, perhaps, in bone or with dapto

in the lung.

So the supporting evidence for each drug may be different based on its specific characteristics and, as is in the package label for daptomycin right now, there is a specific notation regarding pulmonary infection.

So my comment is only to qualify the degree of supporting information that we would need for these drugs.

DR. LEGGETT: Thanks for the qualification. We know that we have clindamycin and vancomycin already approved and they don't get into the CNS. So I think the thing can be said about a lot of drugs.

No. 4; Should CRBSI have its own indication or should this indication be subsumed into a more general PBSA indication? If it is a separate indication, what additional information in the treatment of serious Staph aureus infection should be available to support it?

When we were talking about the complicated versus uncomplicated before, and Barth was saying,

well, let's put--whether they have got a catheter or not, they go into the uncomplicated, I think that, you know, one way to sort of work on this catheter-related bloodstream infection might, in fact, be to study it first in Staph aureus and then attack coag-negative Staph or other sorts of things afterwards, after people got some experience with--because I think the way you are going to treat the catheter with Staph aureus in a coag-negative Staph can be different.

Chris?

DR. OHL: Agreed.

DR. LEGGETT: Now, that was succinct.

John?

DR. BRADLEY: I will the loyal opposition here. I am certainly flexible. I think catheters represent a persisting site of infection and, in some of the patients that I treat, they have had multiple catheters and we just don't have another site to put the catheter in. So there is some interest in trying to treat through a catheter infection.

I would really like a drug that could do that. In addressing Chuck's picture with that catheter infection where we would all automatically pull that, if there is a drug that comes along that gets into biofilm well, that may not be our subsequent direction in catheter-related infections so that you might not need to pull the catheter.

If we set things up so that the catheters are automatically pulled, then--

DR. LEGGETT: I don't know that we need to do that. I think that is something that the FDA would work out with the drug company when they designed what they were going to do in terms of laying out the thing rather than sort of in a broad mode.

Alan?

DR. CROSS: I would just like to emphasize again, which is all the more reason to separate out Staph aureus from Staph epi. Again, I treat patients who are so compromised that they haven't seen a neutrophil in months, that they have coagulase-negative bacteremia and we treat through

it all the time, and it resolves very, very quickly as opposed to Staph aureus.

So I think, in all this discussion, we should really be focusing on Staph aureus and Staph epi should be separate.

DR. LEGGETT: I propose that we rename the Question No. 4 into CRBPSA indication.

Chris?

DR. OHL: As far as, and I am not sure this is an answer, but moving it into its own indication within what we have been calling the primary bloodstream for Staph aureus, is that--what this is going to end up doing probably is when you are moving things into the overtreatment end of things rather than--so that is going to have to be in the consideration because, if you are looking for an entity where a removable focus such as this can be done, with a quick shorter course of therapy, this is probably going to be about it.

If you merge it into the primary bloodstream-infection aspect, isn't that going to make that harder to do? That would be my only

comment.

DR. LEGGETT: The quandary, I think, is pointed out by the fact that many of the people who have a Staph aureus catheter-related infection go on to have complications whereas, some people, you pull it in and there is no problem. But we don't know that a priori. If we allow an indication for catheter-related Staph aureus infection, and somebody shows that and they luck out or the people are chosen so that they find out a way to make that easy group, then we are going to be stuck with complicated problems later on that we don't want.

DR. OHL: Just to clarify. That would then say that it would be mergable.

DR. LEGGETT: It would be merged.

John, Janice, do you guys need anything more on 4 or do you want anything more on 4?

DR. SORETH: We have the practical issue of having guidance for catheter-related bloodstream infections on the web, although all guidances are drafts, but--

DR. LEGGETT: So, in other words, somebody

probably is already studying it and we are pulling the rug out from under their feet.

DR. SORETH: If it is on a respirator at this point, do we revive it somehow or do we pull the plug--the guidance, that is, not the patient.

DR. LEGGETT: Right now, I am not going to the catheter-related bloodstream infection. Is there another question down the road that we can then address that?

DR. SORETH: Okay.

DR. LEGGETT: And just stick this with the Staph aureus.

DR. SORETH: Okay.

DR. LEGGETT: So that was 4(a) and we will come back to 4(b).

No. 5; can data on catheter-related infections--okay, now we have headed into the Staph aureus--do you want to stay with Staph aureus and do preclinical stuff and then switch over--okay.

No. 6; given that bloodstream infections due to Staph aureus have the potential to cause serious morbidity and mortality, what types of

preclinical and early clinical information should be available prior to initiating large clinical trials?

Alan?

DR. CROSS: Well, I think it was already alluded to, but I would hope that there would be some data on clinical efficacy in less serious infections; that is to say, I don't think that the first clinical trial with a new agent that we don't have much information about ought to be in complicated Staph aureus bacteremia.

In the case of Staph aureus, it is particularly important because, although we can accumulate lots of in vitro data, one thing we really didn't talk about is that animal models for Staph aureus are really problematic. People have been trying for years and years and there still is no good animal model.

Even with all the caveats for the applicability of animal models for disease in general, it holds particularly in the case of Staph aureus. So I think that, before going to

complicated infection, we should, at least, have some clinical efficacy in less severe infections.

DR. LEGGETT: Regarding the preclinical stuff, I think that the Staph aureus mouse thigh model has been around since the 40s. And there is still some question with some drugs whether you are looking at mice that can't walk to get water and eat and that is why they die, because their thighs swell up to everything, or the drug doesn't work. So it is going to have to more than just one model.

The other problem is that the models often have very limited time frames. There is the example I gave of the vancomycin. No matter what drug levels you get, you get static CFUs until 18 hours and then, boom, it falls off the curve. So, it depends. If you had looked at it 12 to 18 hours, you would say the drug doesn't work. If you carry your therapy on to 36 or 48, it works.

So I think that you are going to want to have a variety of stuff. The trouble with the rabbit--the trouble with any osteomyelitis is how far out you go and whether you have got good dosing

regimens. Remember that the only way you are going to get that is you take a pair of pliers and break their leg and then you squirt bugs in their blood. That is the way you get the osteomyelitis model.

I think in terms of endocarditis models, the rat is what I would sort of refer to as a right-sided model. The rabbit would be a left-sided model. They need to be done well and so that you don't just get a drop from 8 logs to 5 logs and that is clinically significant.

So I think that the model data is going to have to improve but there are a variety of existing models that certainly should be looked at knowing their intrinsic problems before we go into this.

Any other thoughts of folks? Any other thoughts about early clinical information? I would agree with Alan that what we want to see first is simple stuff, uncomplicated skin and soft-tissue, UTIs if it is renally excreted and that sort of stuff.

DR. POWERS: Jim, could you ask folks to comment on the bacteriostatic versus bactericidal

issue and is that distinction even useful?

DR. LEGGETT: Any ideas? My take on it is that it has never been quite as clear as we have made it. It we give more and more TNP sulfa and more and more clinda and, for some bugs as opposed to other bugs, they are cidal instead of static and that sort of thing. I think it is often a question of we have got white cells and we lived a long time before antibiotics even if we are not chewing on chinchona in the Amazon.

But I think it is a question of how much drug gets to the site and is it enough that it will--even if it holds down bacteria, the white cells will take over, or does not enough get there. I don't know that a simple, oh, this is cidal but we only gave it two times in the MIC and it didn't work versus, it is static but we gave it 12 times in the MIC and it worked.

Alan? Tom, did you want to say something, too?

DR. CROSS: I mean, we already have the example of the timeless classic, Keflin. It is

not efficacious in the treatment of Staph aureus endocarditis.

DR. LEGGETT: Barth?

DR. RELLER: I would just emphasize that it is not that a drug is cidal or static. It is how the testing is done and which organism you are talking about. So what is static for one may be cidal for another.

I think it is important, though, not to disregard to conceptual importance of having bactericidal activity for certain kinds of infections, namely, meningitis and endocarditis where one is really--I mean, you are dependent upon the drug and, in the case of endocarditis, the adjunctive complementary surgical therapy.

So you don't have to get rid of the concepts if one recognizes that drugs--I mean, chloramphenicol is bactericidal for the pneumococcus unless it is penicillin-resistant. I mean, it doesn't necessary follow logic but it is true if you look at the complexity of the issues and the interactions and the methodology for doing

it.

Another example is Staph aureus. Nafcillin is cidal for Staph aureus but it can be very hard to show that depending on whether you do it in plastic or whether you do it in glass, et cetera. So there are methodologic issues and one just has to beware of rubbish.

DR. LEGGETT: And playing tonic versus adhered bacteria. No. 7; how many positive blood cultures are required prior to study entry in clinical trials of bacteremia Staph aureus?

Sorry, John. You have got to raise your hand louder.

DR. BRADLEY: I will work on that one; the next guidance document. In addition to meningitis and endocarditis, I though John had brought up neutropenic hosts. I think, again, traditionally, we wouldn't want to go there. A neutropenic host still has macrophages and opsonizing antibodies so it is not an all-or-none phenomenon.

But I think before I would study a drug in neutropenia, I would, for sure, like to make sure

it works in someone with white cells. The idea of bacteriostatic and bactericidal, certainly I agree with Barth, it is a spectrum. Based on the mechanism of action, some drugs are certainly more rapidly cidal no matter what system you put them in. The more severe the infection, the more life-threatening, the more bactericidal I would like the drug to be when I am treating a patient.

But the ultimate outcome, the endpoints that we measure, are the best way to find out whether the drugs are equivalent or not.

DR. LEGGETT: My point was taking it to the statement that I wouldn't say, no, you can't study it because your drug is "static."

So how many positive blood cultures do we want before clinical trials? Don is giving the victory sign.

DR. PORETZ: Two.

DR. POWERS: Could we qualify where those two are coming from, as central line versus peripheral?

DR. PORETZ: If someone is clinically ill

and septic and you draw it from the central line, or even the peripheral, why would you assume it is not significant?

DR. POWERS: Barth, I think you actually did this with Mel Weinstein. I think there was an article that you wrote about trying to correlate catheters and peripheral stuff, if you want to comment on that.

DR. RELLER: That one was with Richard Everts, one of our fellows. It just looked at simultaneously obtained blood cultures from peripheral venous puncture and then different categories of catheters including arterial to look at the likelihood of contamination. The least is with the peripherally drawn.

I mean, I agree that two are necessary. The guidance document related to the coag-negative permitted one through if there were a validator peripherally. When a catheter is not removed, you could have one through the catheter and one peripherally. I think one could even go so far as, in those patients with lifelines, to have one

through the catheter that could not have a peripheral if one had confirmation that was concrete; for example, C.T.-guided aspirate of an abscess or from the bone.

Usually, one would be able to have a peripheral. But I am just trying to think of what situations would you not be able to have that second blood culture.

DR. PORETZ: You have no access to drawing blood. I guess you could do a femoral-artery stick, but sometimes there is no venous blood that you can draw in a lot of these people. You just don't have access to it. So I guess you could get an arterial line, but if someone was clinically septic and you had Staph aureus grow out of the central line, that should be fairly valid as to the cause of why they are looking septic.

DR. LEGGETT: Repeatedly, I buy that for Staph aureus.

DR. PORETZ: Well, I am talking about--the question says PBSA.

DR. POWERS: So then, when we talk about

two blood cultures drawn through a central line, we would assume that that means--you know how this happens in practice. You send the medical student in, he draws a big vat of 60 ccs out and fills out ten blood-culture bottles and sends them off to the lab. True; right?

So the question would be that would be two blood cultures separated in time by some amount so that we are actually getting two distinct measurements?

DR. LEGGETT: Jan?

DR. PATTERSON: Well, my comment is that I think you want at least one peripheral blood culture positive. The problem with, like you said, in getting it from the catheter only--I mean, it may well be the source of infection but it may not be, particularly in somebody who might have something--diverticulitis or something else going on in their bowel.

I don't think, with Staph aureus bacteremia, it is not like Strep viridans in that we are going to draw a culture and then wait six

hours and then get another culture. So a lot of times, you end up getting two sets at the same time, and is that meaningful?

Like two sets, like you are talking about from the same catheter site at the same time, are not really meaningful. Yet you don't want to wait another hour or two on that patient to start antibiotics.

I think the ideal thing is that you would want one from the catheter and one peripheral. If you had those two positive, even if it was at a single point in time, that would be okay. I just don't think that it is realistic to say we are going to wait two or three hours to start antibiotics to get another culture.

DR. LEGGETT: Let's not just talk about catheters. Let's also talk about just plain old primary--you know, the Staph aureus. So we don't have a catheter, or we have got a burned-out I.V. drug user and we have no access, those kind of hemodiabetic, peripheral vascular disease, dialysis person who has used up all his vein grafts.

DR. PATTERSON: I think if you can't get a peripheral blood culture in a patient without a catheter, you can't put them on the study.

DR. LEGGETT: Barth.

DR. RELLER: I would like to emphasize that there is a difference, obviously, between what would be acceptable, though, to initiate therapy in a sick patient. But I think it is something different for the specificity required to rigorously assess a patient in a clinical trial that would stand the test of time.

I think that, if you can't get the blood cultures and have two independent acquisitions of blood, not this two through the same catheter or one blue lumen, red lumen. I agree completely with Jan that that is just not somebody that is going to be able to be enrolled in the trial.

DR. PORETZ: Can I say one thing?

DR. LEGGETT: Yes.

DR. PORETZ: You can--why not, if it is not available on the venous site, do an arterial site. Why should that exclude a patient from a

study if you can get an arterial puncture, culture.

DR. RELLER: I am just arguing for two independent collections of blood.

DR. PORETZ: Fair enough.

DR. PATTERSON: Yes; I didn't say peripheral venous. I said just peripheral.

DR. LEGGETT: Chris?

DR. OHL: Just to clarify. Would that be, then, either single site, two points in time or one site, two cultures or--I am not saying that right--same site, two points in time or two different sites at one point in time.

DR. LEGGETT: Either one.

DR. RELLER: If one had the same vein and you went into twice with independent preparations, it would be an unusual situation where you would have to do that, but that would be acceptable. It is the independence that is critical. This is, of course, much more an issue with coag-negative Staph than Staph aureus because there are few Staph aureus that are contaminants. But it is not zero. So, consequently, for clinical trials, I think one

needs to adhere to two independently obtained blood cultures.

DR. POWERS: I don't think this is going to be an insignificant issue because I know, when I am on service at NIH, one of the biggest problems that I have in seeing patients is the fact that blood cultures are routinely drawn through central lines only as a matter of convenience.

Having done my residency at a place that had no blood drawing, I know you can get blood out of a stone. So, if their heart is pumping, you can get some blood out of them somewhere. But that is not what happens out there. We know that a lot of this is done out of convenience, that people will draw multiple blood cultures out of the line.

So I just want to bring this up that that may become as big an issue as getting data from a catheter when all we are going to have in these patients is data from blood cultures drawn through a catheter without any peripheral data to go along with it.

DR. LEGGETT: Enough. Uncle. Let's turn

our attention to the catheter-related bloodstream infections not due to Staph aureus. Should it have its own indication or should this indication be subsumed into a more general indication? If there is a separate indication, what additional information should be available? Can we phrase it that way? Is that going to help you?

In terms of thinking about this in a catheter-related blood-stream infection, to try to help companies get adequate people in, I think we have to remember that we have got to be able to try to fashion a trial for some sick people without taking away folks who have entered into a trial of a drug that they aren't sure is going to work, and then we take that away from them so they have got nothing.

So I would have a hard time pulling back and saying, no; we can't do that. I think we have got ourselves into it and we have got to figure out a way to do it. The two sides of the pros and cons, I think, sort of wrap that up but I think we need to find a way of tightening up the ship if we

can in the next half an hour.

DR. CROSS: Again, I will just expand on the comments I made earlier about how very different catheter-related Staph aureus infections are from coag-negative. Again, I deal with patients who have central catheters in and the oncologists work in a setting where any fever, like 99.8, is taken as an indication of occult sepsis even if the patient is reading a newspaper. They will start therapy based on that alone with, it turns out, a not unreasonable expectation that they will have coag-negative Staph.

On the other hand, once we are called in, they ask whether or not they can treat through the probably catheter-related sepsis. It turns out we have done this and it is not only that we have done this, but usually, once we start, most often, vancomycin, the fever resolves. We get a blood culture 24 hours later and 48 hours later and it has cleared so there is both the clinical and microbiologic clearing and, within five days, it has been our practice that if everyone responds to

simply stop therapy and observe them based on the observation that, if they relapse, so be it. We will know and we can always restart.

It is really an extrapolation of what we do at the other end which is that, for empiric therapy, we don't start vancomycin on Day 1 because the teaching is that you always have time to wait for your blood cultures in the case of Staph epi so you don't need empiric therapy.

So we have just reversed that with the idea that, if it is not urgent, to start at the outset when we have time that maybe we have time to wait for a relapse. As I said, the duration of therapy in that situation for Staph epi has been very, very different from Staph aureus which is why I think we do need to study them separately and, perhaps, not extrapolate from how we practice with Staph aureus to how we practice with Staph epi.

Furthermore, if you just look in Bergey's Manual at the various virulence factors associated with Staph aureus versus what you see with Staph epi, it is a full page versus a few lines.

DR. LEGGETT: Do we then fashion this trials bug-by-bug or if somebody has a drug that works against Gram-positives and Gram-negatives, do we let them take all comers even though there are not going to be very many Enterobacters? Any thoughts Jan?

DR. PATTERSON: Well, my comment was going to be that I think the modification of the guidance should be for Staph aureus and really just Staph aureus, for one thing to differentiate it from the other Gram-positive bacteremias like coag-negative Staph and to allow this category of primary bacteremia, including catheter-related bacteremias, and with the definition of primarily being no source of infection after echo, chest X-ray, perhaps C.T. abdomen with contrast and to allow the 48 hours of antibiotics.

My read on it is that the modification should just be for Staph aureus primary bacteremia.

DR. LEGGETT: Do we allow trials currently going on to then open up to bacteremias after they are fashioned or--what do we do with these people

that have already given of their time?

DR. PATTERSON: That may be more of a question for Tom and Joan.

DR. HILTON: The only comment I would like to add to that is if there is highly different prognosis for different bugs, then I would keep them separate.

DR. LEGGETT: Does anybody have any more comments about coag-negative Staph catheter-related?

Chris?

DR. OHL: I assume this is in the purview of Question 5.

DR. LEGGETT: Yes; 4(b) and 5.

DR. OHL: As far as including catheter-related infections as a subset of complicated skin infections, for the issues of the two different organisms, there is one big difficulty that I have problems with. The other issue is that a lot of catheter-related infections have nothing to do with the pathophysiology of skin and soft-tissue infections.

If you are including just tunnel infections, possibly, but I am not so sure that was the implication of this question. So I would say no. But, having said that, we do need to find something for the ongoing trials that are being done.

DR. LEGGETT: Although, if we are talking about coag-negative Staph, I mean, there is only one place it came from. So you could have the drug--it is going to warrant a study if it is Gram-positive. It is going to warrant a study in skin and soft-tissue infections, anyway, and the label could then say complicated skin and soft-tissue infections including catheter-related bacteremia, or something--catheter-related bloodstream, or catheter-related infections, even though the pathophysiology may--it is sort of more of a portal of entry focus then. It is the same thing, cause, in cellulitis.

Jan?

DR. PATTERSON: I think you can have a catheter-related infection without bacteremia and a

tunnel infection being an example. I my mind, that would fit with a complicated skin infection. I don't think you see it that often, but, I mean, it is possible.

DR. LEGGETT: John?

DR. POWERS: Could I ask folks to make that distinction, though? Chris brings up a good issue about the picture that we were shown is essentially a tunnel infection where you are seeing the erythema march along the area where the catheter is underneath the skin. Probably much more common, though, are exit-site infections where you just see some erythema around the outside or even what gets more confusing is the patient had some tape around there, and they took the tape off and now there is a little redness there and it grows coag-negative staphylococci.

I am trying to get further and further away from the most clear case we saw on that slide. Then there is the issue of what I would like you guys to address about this thing called catheter-tip infections in terms of do catheters

get infected or is it the infection in the person that we are worried about and does colonization of a catheter with no bacteremia and nothing else, how would we analyze that data?

DR. LEGGETT: Barth?

DR. RELLER: If I recall correctly, Dennis Mackey's original article in the New England Journal was to accurately categorize colonized catheters from non-colonized catheters. It had nothing to do with catheter infection.

In our laboratory, we do not culture inanimate pieces of plastic devices, et cetera. We want tissue attached thereto like pocket infections with pacemakers, et cetera. I think the patients are infected. The devices may be the source of infection but of their introduction to the patient or colonization and I would not put--I would just turn it around about 180 degrees and follow up to Jan's comment in addressing this question specifically, and that is cellulitis as a complicated of the catheter, or associated with the catheter, as opposed to catheter-associated

cell--you see what I mean?

It is just a way of thinking about it so that if one had a pacemaker pocket infection, if it is tracking down leads and it is associated with bacteremia, we and others have published on that. That means one thing in terms of removal.

But if it is confined and not egressed into the bloodstream and things are changed and it is debrided and drained, I mean, it could be a cellulitis or a subcutaneous abscess that is related to the device. So I think that those are all variations on skin and soft-tissue infections that, in truth, are related to the catheter.

But I think that we need--or I would advise that, as Alan has emphasized, that bacteremias associated with catheters, with Staph aureus, are different from coag-negative Staph and the rigorous definition for catheter-related blood-stream infections with coag-negative Staph is very important to maintain the integrity of the entity and, where there is not bacteremia, that they be cellulitis, subcutaneous abscess,

soft-tissue, et cetera and, if you want to throw in "related to the catheter," that is okay.

DR. LEGGETT: Alan?

DR. CROSS: I just want to emphasize that, in the Mackey article, the question he was asking is how do we know if you have a positive peripheral culture whether or not the catheter could be implicated.

So, in doing that, you had to have both a peripheral blood culture submitted that was positive and have a catheter tip which, on semi-quantitative culture, were positive. Now, unfortunately, when I make rounds and see the house staff, they are always culturing the tip and never get the peripheral culture.

Then we are asked, what do we do with a positive catheter tip based on a misinterpretation of that Mackey article? The answer is, you throw it away. So the catheter-tip culture is only a tool to help you make some decision on what you have in your peripheral blood culture.

DR. LEGGETT: The other thing is go back

and look at the graph. It was an arbitrary post hoc drawing the line at 15 because, down to 15, he had positive blood cultures. Below 15, he did not. If you look at that diagram, almost all the positive blood cultures are in the "too numerous to count." So maybe we should--the cutoff should be too numerous to count and not 15.

John?

DR. BRADLEY: In a practical sense, a lot of these catheters, when they are pulled out, will be pulled out through goopy exit sites and the catheter, itself, may not be infected. But, once you pull it through it through the site and culture it, unless you do it under the strictest of conditions, you get a false-positive catheter-tip infection.

DR. LEGGETT: Jan?

DR. PATTERSON: I think, in answer to John's specific question, I don't think a catheter tip gets infected. I think it gets colonized and the infection--you are using it to define whether it is a catheter infection.

DR. LEGGETT: Or a catheter as the portal of entry for an infection.

Chris?

DR. OHL: So it is more we are discussing skin and soft-tissue infections secondary to or associated with the catheter rather than the reverse.

DR. LEGGETT: Rather than the other way around.

Any other questions regarding that specific thing? No 5; how many data on catheter-related infections--if we are going to put it with the skin and soft-tissue, it obviously has got to be a peripheral and one through the catheter. I don't think there is any way around that.

No. 8; screening patients for admission in clinical trials is complicated due to factors such as the potential for an occult primary source of infection, to not be noticed, I assume the end of the sentence should read. What advice can you provide regarding a general approach to screening

patients?

In other words, what you are asking--this is back to that "primary bacteremia," or whatever we are going to call it; right? I mean, I think the obvious things that we always do when we sort of work up a fever; you have got to evaluate the lungs, evaluate the urine, look over the skin. I don't know that you have got to see if their back hurts and go there.

I don't know that you have to sort of make a standard for everybody, but I am not so sure that, for a clinical trial, that you might not have to have a minimum of stuff and then you could have things on top of that that would be indicated by what you thought might be going on.

So I don't think we would proscribe somebody getting a C.T. of the belly or an M.R. of spine or X-rays of the ankle or something, but I don't know that we necessarily would have to do all that.

I guess the question is what are we going to do about the echocardiogram stuff?

Yes?

DR. THEILMAN: I actually think that a very intentional strategy should be outlined. Clinicians can get sloppy at times and rely on technology. I think everybody should have a careful joint exam. Everyone should look for splinter hemorrhages, palatal and conjunctival petechiae. Given the ramifications and the context of a clinical trial, I think everyone with Staph aureus bacteremia should have a TEE.

DR. LEGGETT: John?

DR. POWERS: Could I ask a question about--one of the things we discussed internally was what is the added benefit of a transesophageal echo above a transthoracic because we thought that, when it comes to just the ease of doing these trials, I don't know--do all centers have the ability to do transesophageal at this point?

DR. LEGGETT: We all support our local cardiologists.

DR. POWERS: Then there is the issue of if you get a transthoracic and it is positive,

obviously, you don't need the transesophageal. So could folks address that difference and what incremental benefit would there be in taking people who get negative transthoracics in making them get a transesophageal.

DR. LEGGETT: With the risk of complications.

Barth, do you want to expound a little bit?

Personally, if I have Staph aureus bacteremia and he looks like Don's patient, I don't even get an echocardiogram because I am not going to change my therapy. But I keep watching them, make sure their P.R. interval doesn't start doing things. Then, if I am starting to get worried, if they are looking bad, then, at that point, if it is going to give you some added information, like going to the O.R., whether that is transthoracic or transesophageal, that is where it helps me.

But I, personally, don't even get them with Staph aureus bacteremia.

DR. POWERS: I think, though, that that is

the issue that we are going to have to deal with here. Even if you have a very sick-looking patient, we are going to need some specificity of that diagnosis to call that person endocarditis or not. So, even if you have a high clinical suspicion, we would still need some kind of data to be able to call that person endocarditis and would, in that case, a transthoracic be okay.

DR. LEGGETT: And then, if the trial comes out, you are going to be driving clinical practice into that area again. But, I think, for the purposes of a clinical trial, it is a little bit different than clinical practice.

Barth.

DR. RELLER: To me, there are three components; the clinical trial, clinical practice and the severity of how the patient presents. Coupling Don's earlier comments and Nate's now, I think all patients entered into such a trial would have to have the two independent Staph aureus blood cultures. If a thorough physical examination and history, in the setting, not a chronic dialysis

patient, et cetera--in other words, from the literature, a low-risk patient for complications, I do not think that every one of those needs a TEE.

If one has a transthoracic that is positive, obviously, in good hands, it is superfluous to get the TEE. But, I think, clearly, the literature and everyone here would agree that to have the full sensitivity, one needs a TEE. So a sick patient who has got rumblings, when there is noise, when there is smoke, I think you need a TEE.

So it is a matter of categorizing the patients, that if there are no leads of any kind, I think it would be going too far to say two positive blood cultures, catheter in place that is removed, looks uncomplicated. Some clinicians would give two weeks if the patient's temperature comes down immediately, their white count is okay, their physical exam and you follow them and you see them each day and everything is okay, to say everyone of those needs a TEE? I think that would be going too far.

DR. POWERS: Should they get some echo,

though, or none at all?

DR. RELLER: I can't quote the numbers. Maybe Don, others, Al, could help. I think there are some figures in terms of the economic--is it better to do the less expensive transthoracic and then follow up only the negatives with the TEE or is it better to separate the patients who should have a TEE or not have a TEE and just go for the one that is the most sensitive and skip the intermediate step?

I can't remember the data on that, but I think that has been looked at, maybe not as thoroughly and carefully as it should. My preference is to either get it or not get it and not get it halfway. That is my opinion.

DR. LEGGETT: Chris?

DR. OHL: It showed, I think, though, that in that setting of that patient that you described with the catheter removable focus and such where one might go for shorter-course therapy that, in that setting, a TEE should be done in order to rule out cult endocarditis before committing to that

shorter course.

So, in that particular setting, I would say that echocardiograms for the purposes of study, which may be different than clinical practice, I agree--but echocardiograms for purposes of study should be done. TTE is okay if positive. If not, TEE.

DR. LEGGETT: To follow up on the point. Even the physical exam on the form to fill out can have a sign that says, splinter, check yes or no. I mean, we are going to tell them what they have got to do. It is not going to leave it up to whatever they feel like doing.

DR. POWERS: Even in that person, isn't there some literature that says that size of the vegetation may have some impact on outcome. So, in those people, it might be useful information to get the echo. I guess I want to go back to what I tried to bring up this morning that, if we leave the decision about what kind of workup to get, echo or no echo, up to investigator discretion, what we are going to be measuring is just that,

investigator discretion and we will have very distinct populations of people.

The people that Dr. Poretz described has, perhaps, Staph aureus in his blood. Whether he has endocarditis or not is a completely different question to answer. But we know that there are clinicians who will behave as if, oh, the patient looked really sick; therefore, I am going to treat for four weeks, whereas the same exact--different clinician, same E.R., would treat that guy for two weeks.

DR. LEGGETT: Okay. Agreed.

Jan, we have got five minutes left.

DR. PATTERSON: I was just going to some of us talked about the importance of an endocarditis indication and, if we really mean that, then I think we are unrealistic if we are only going to use the criteria for definite endocarditis with echo. So I think we have to include patients that have probable endocarditis in that as well.

DR. LEGGETT: Agreed.

We have talked about this a little bit before. Should patients with an identified focus be entered/remain in trials? We sort of talked around this before. Does anybody have anything more to say? And is endocarditis a special case? We talked about keeping the endocarditis in the bacteremia trial.

In the brief time that remains, unless anybody has any other questions, or you guys have any questions of us--

DR. FLEMING: On this point?

DR. LEGGETT: Or on any. Speak now or forever hold your peace.

DR. FLEMING: In PBSA, if you knew the primary site, then, technically, this person is not in your eligibility criteria, I assume. So, if you knew it advance, I am assuming you wouldn't enter the patient unless you were wanting to look at an issue broader than PBSA.

The issue, though, is what if you don't know it at baseline and you find out subsequently it is skin or something, is that the other part of

your question? I mean, I certainly would hope that, unless there is available information indicating lack of efficacy in such a patient, I would certainly presume that it would be most logical to continue treatment and to analyze the results in those patients.

You may want to do subsequent analyses that would include or exclude that patient but I would encourage, if you found out post-baseline the source that you hadn't know before that you continue to follow that person through.

DR. LEGGETT: Quick.

DR. CROSS: I just want to make one fast obvious point. I was impressed with all the presentations this morning that, despite 40 or 50 years of study, how little prospective controlled studies we have. And then, after having seen the difficulty of enrolling this patient population, I would just like to make plea that rather than wait until we have the perfect clinical design that at least we have some feasible design which allows rigorous analysis but allows us to enroll patients

at least as a first step so we could get some experience and know how to refine that rather than to be stymied for that perfect trial.

DR. LEGGETT: Janice?

DR. SORETH: I think, as always, better can be the enemy of good or fair.

As we wrap up, I just wanted to make note of the fact that this is our last advisory committee meeting that Dr. Jim Leggett is chairing as he is rotating off in November, and also Dr. Cross, your tenure with us also comes to an close and in recognition of two colleagues who are not here at the table, Dr. Steve Ebert and Dr. Julio Ramirez.

We thank you very much.

DR. LEGGETT: Thank you.

Summary

DR. LEGGETT: In summary, first of all, I would like to thank the speakers for their presentations and the committee members for their efforts and their tolerance of my idiosyncracies and my bad puns.

Today, we have discussed many complex issues related to trial design and analysis in studying Staph aureus bacteremia and catheter-related blood-stream infections. We heard the regulatory history of bacteremia indications. We were updated on the epidemiology of Staph aureus bacteremia and we learned of new microbiological diagnostic techniques in the diagnosis of Staph aureus bacteremia.

We debated clinical-trial issues with Staph aureus bacteremia without reaching a final consensus but, certainly, we were cognizant of why a great trial studying Staph aureus bacteremia has yet to be done.

In the Open Public Hearings, we saw the difficulty of enrolling patients in a bacteremia trial and heard of design issues in catheter-related infection studies. We heard of issues relating to studying catheter-related blood-stream infections this afternoon and, again, tackled with the reiteration of the current CRBSI, or at least an attempt to, guidance document.

I would like to thank you all for your patience and the meeting is now adjourned.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)

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