U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

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67TH MEETING

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Wednesday, October 20, 1999

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The meeting was held in the Kennedy Ballroom, Holiday Inn, 8777 Georgia Avenue, Silver Spring, Maryland, at 8:00 a.m., William Craig, M.D., Chairman, presiding.

PRESENT:

WILLIAM CRAIG, M.D., Chairman

RHONDA STOVER, R.Ph., Executive Secretary

GORDON L. ARCHER, M.D., Member

P. JOAN CHESNEY, M.D., Member

CELIA D.C. CHRISTIE-SAMUELS, M.D., M.P.H., FAAP, Member

ROBERT L. DANNER, M.D., Member

BARBARA E. MURRAY, M.D., Member

PRESENT (Continued) :

CARL W. NORDEN, M.D., Member

JUDITH R. O'FALLON, Ph.D., Member

JULIE PARSONNET, M.D., Member

BARTH L. RELLER, M.D., Member

DAVID E. SOPER, M.D., Member

KEITH A. RODVOLD, Pharm.D., Consumer Representative

GARY CHIKAMI, M.D., FDA Representative

SANDRA KWEDER, M.D., FDA Representative

FREDERICK MARSIK, Ph.D., FDA Representative

DAVID ROSS, M.D., FDA Representative

ROBERT HOPKINS, M.D., FDA Representative

MARK GOLDBERGER, M.D., FDA Representative

LEONARD MERMEL, D.O., Sc.M., Consultant

DAVID BATTINELLI, M.D., Guest Expert

LEIGH DONOWITZ, M.D., Guest Expert

MELVIN WEINSTEIN, M.D., Guest Expert

CYNTHIA WHITNEY, M.D., M.P.H., Guest Expert

GRAHAM BURTON, M.D., Speaker

KAREN BUSH, Ph.D., Speaker

MICHAEL CORRADO, M.D., Speaker

EDWARD COX, M.D., Speaker

PRESENT (Continued) :

ANTONE A. MEDEIROS, M.D., Speaker

PUBLIC COMMENT:

RAY ZHU, Ph.D.

ISAAM RAAD, M.D.

DR. DAVID BELL

ALSO PRESENT:

CHARLES M. FOGARTY, M.D.

GEORGE ELIOPOULIS, M.D.

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:13 a.m.)

CHAIRMAN CRAIG: I'd like to welcome you to the 67th meeting of the Anti-infective Drugs Advisory Committee.

The agenda this morning is going to be on the development of antimicrobial drugs for the treatment of catheter related bloodstream infections.

What I'd like to do is go around the room and have everybody give their name and their affiliation so that we can get all of the people at the table onto the official record. You need to push the little light by your speaker in order for it to turn it on so that you can be recorded.

We'll start over there with Barth.

DR. RELLER: Barth Reller, Duke University Medical Center.

DR. MURRAY: Barbara Murray, University of Texas Medical School, Division of Infectious Diseases.

DR. ARCHER: Gordon Archer, Medical College of Virginia Campus of Virginia Commonwealth University.

DR. CHESNEY: Joan Chesney, University of Tennessee, Memphis, Department of Pediatrics.

DR. O'FALLON: Judith O'Fallon, Mayo

Clinic.

DR. RODVOLD: Keith Rodvold, Colleges of Pharmacy and Medicine, University of Illinois in Chicago.

DR. CHRISTIE-SAMUELS: Celia Christie, Department of Child Health, University Hospital of the West Indes, Jamaica.

DR. SOPER: David Soper, Medical University of South Carolina in Charleston.

DR. DANNER: Bob Danner, Critical Care Medicine Department, NIH.

MS. STOVER: Rhonda Stover, FDA.

CHAIRMAN CRAIG: Bill Craig, University of Wisconsin.

DR. PARSONNET: Julie Parsonnet, Infectious Diseases at Stanford.

DR. NORDEN: Carl Norden, Infectious Diseases, Cooper Hospital, University of New Jersey Medical Center.

DR. WEINSTEIN: Mel Weinstein, Robert Wood Johnson Medical School.

DR. DONOWITZ: Leigh Donowitz, Pediatric Infectious Diseases at the University of Virginia.

DR. MARSIK: Fred Marsik, FDA microbiologist.

DR. ROSS: David Ross, FDA, medical officer.

DR. CHIKAMI: And I'm Gary Chikami. I'm the Director of the Division of Anti-infective Drug Products at the FDA.

CHAIRMAN CRAIG: Next we'll have Rhonda Stover read the conflict of interest statement.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that since the issues to be discussed by the committee will not have a unique impact on any particular firm or product, but rather may have widespread implications to all similar products, in accordance with 18 United States Code 208(b), general matters, waivers have been granted to each special government employee participating in today's meeting.

In the event that the discussions involve any other products or firms not already on the agenda in which an FDA participant has a financial interest,

the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon.

CHAIRMAN CRAIG: Thank you, Rhonda.

Next, Gary Chikami will give the FDA introduction.

DR. CHIKAMI: Does this work?

Since we're running a little bit behind schedule, I'll be brief. This morning's session is an outgrowth of two activities within the Division of Anti-infective Drug Products and within the Office of Drug Evaluation IV.

The first is the ongoing process that's been developed to write guidance documents on many of the clinical issues, clinical trial issues, that we deal with in drug development in this area.

And as most of the people in this room will recall, about a year and a half ago in July, we had a three-day meeting to discuss many documents.

The second is a discussion we had just about a year ago on the development of products

specifically for antibiotic resistant organisms, and at that discussion there was a look at some new indications which are associated with resistant organisms and how the division and office might move forward in encouraging development of products in these areas.

The status of the guidance document that will be discussed at this point is that it's a draft. We certainly look forward to the committee's discussion, both general topics on this guidance document, and we'll have some specific questions.

In addition, there will be an opportunity for the public to make comments at this meeting, but in addition, the draft document will be published in the Federal Register, and we'll request formal public comment by that mechanism as well.

so I think there'll be plenty of opportunity for both the academic community and industry to provide us with comments on this document.

What I'd like to do now is change gears a little bit. Three of our committee' members will be rotating off this year, and I think that we appreciate sort of the expertise that this committee provides to the division in both regard to product specific issues, but in general scientific and clinical issues,

as much of the discussion this morning will involved.

And I'd like to present these three members with tokens of our appreciation that sort of speaks to their service to the agency and to the government.

The first person is Dr. Julie Parsonnet, who's from Stanford.

Thanks very much.

DR. PARSONNET: Thanks.

DR. CHIKAMI: The second is Dr. Carl Norden.

Thanks, Carl.

DR. NORDEN: Thank you.

DR. CHIKAMI: And the final person who's rotating off in this term is Dr. Craig, who has been the chair of this committee, and we certainly appreciate his tenure and his sort of steady guidance to this committee.

Thank you.

CHAIRMAN CRAIG: Thank you very much.

DR. CHIKAMI: And with that I'll turn the chair back over to Dr. Craig.

CHAIRMAN CRAIG: Thank you, Gary.

We'll go on then actually on time, even ahead of time, for David Ross' FDA presentation.

DR. ROSS: I think the obligatory first question is: is this thing working? And it seems to be.

My name is David Ross. I'm a medical officer in the Division of Anti-infective Drug Products, and I'm going to be presenting the draft guidance on catheter related bloodstream infections, developing antimicrobial drugs for treatment.

Next slide.

What I'd like to do in the next 20, 25 minutes or so is start with a regulatory perspective for this entity and then go over the details of the proposed guidance.

Next slide.

In terms of the background for this indication, prior to 1993, the Division of Anti-infective Drug Products granted the indication of bacteremia, and some important points that I want to note about how this indication was studied and granted was that sponsors would submit data on patients with any sign of infection who had a positive blood culture. So this was not studied as an indication in its own right, but rather, data was pooled from other studies.

And one paradigm that was used was to

define patients with one positive blood culture as having bacteremia and two positive blood cultures as having septicemia.

Well, in 1993, the advisory committee discussed this issue and expressed a number of concerns over this indication, specifically, the lack of specificity of the disease definition; the problems inherent in pooling results from different sites of infection; and what the true clinical implications of a positive blood culture are which might differ depending on whether the pathogen was Pseudomonas aeruginosa or coagulase negative Staphylococci.

And the recommendations of the committee at that time were to drop bacteremia and septicemia as primary indications, but to retain bacteremia in labeling in the context of infections at defined sites of infection, for example, pneumonia with concurrent bacteremia.

Next slide.

Well, what's happened since then?

Currently estimates of incidence of catheter related bloodstream infections are such that there's around **400,000** of these infections thought to occur annually in this country, and as Dr. Chikami mentioned, a year ago the advisory committee discussed

this issue and noted the increasing incidence of catheter related bloodstream infections, the high attributable morality and morbidity associated with these infections, the fact that these infections are associated with resistant pathogens, and, last but not least, the lack of controlled clinical trial data on treatment of these infections.

And the recommendation of the committee at that time was to consider catheter related bloodstream infections as a new indication.

In accord with that recommendation, a working group was formed within the Division of Anti-infective Drug Products to write a guidance for industry for development of antimicrobial drugs for treatment of catheter related bloodstream infections.

Next slide.

And our goals that we had for the working group were given the lack of pathomneumonic signs and symptoms and the previous problems in terms of disease definition with bacteremia, to construct a specific but flexible disease definition, to provide clear guidance to sponsors with respect to who should be studied, how efficacy should be assessed, and how data should be analyzed.

And finally, to allow for extension to the

very important issue of catheter related bloodstream infections in the pediatric population, as well as non-bacterialcatheterrelatedbloodstreaminfections.

Next slide.

When we moved to an overview of the guidance, I'm going to start by giving the disease definition that has been constructed; talk about general study considerations; move on to proposals for who should be studied; and describe clinical inclusion criteria, microbiologic inclusion criteria, and exclusion criteria; discuss how efficacy should be assessed in such studies; and finish with analytic and statistical considerations.

Next slide.

So how do we define this entity? Catheter related bloodstream infections are defined in the proposed guidance as bloodstream infection resulting from an infected vascular device or contaminated infusate.

And the sort of devices that would be included would include central venous catheters; tunneled catheters, such as Hickman's; non-tunneled, short term central venous catheters, and subcutaneously implanted devices, such as Porta-caths.; peripherally inserted central lines; dialysis

catheters, such as Quinton catheters; Swann Ganz catheters; peripheral arterial catheters; and peripheral venous catheters; would include other devices, such as prosthetic cardiac valves, vascular grafts, and ventricular peritoneal shunts.

Next slide.

In terms of general study considerations, with respect to obtaining substantial evidence of safety and efficacy for registration purposes, we would recommend two adequate and well controlled studies, although a single study might be sufficient under conditions outlined in the agency's clinical effectiveness document.

We recognize that studies will make use of an active control, and depending on whether the control regimen has evidence of effectiveness, one will choose a superiority or an equivalence design, and I'll talk about that later on.

A double blind design is preferred.

Because of the need for empiric therapy, studies can enroll patients without microbiologically proven catheter related bloodstream infections, but the major emphasis will be on those patients with clinicallyandmicrobiologicallydocumentedinfection.

Next slide.

So who should be studied?

Well, clearly, patients with catheter related bloodstream infection, but not patients who have other sources of bacteremia either from other endovascular infections or bacteremic infections at other defined anatomic sites.

In addition, because we're interested in the treatment effect of antimicrobials, we would exclude patients who are treatable by line removal alone.

Next slide.

So with respect to defining the study population, clinically patients could be enrolled if they had either systemic evidence of infection or localized evidence of catheter related infection.

And the criteria we would propose for systemic evidence of infection would be an alteration in temperature, fever or hypothermia, with one of the following: altered white cell count or white shift; tachycardia; tachypnea; or hypotension.

Alternatively, patients could be enrolled if they had signs of local -- localized signs of infection, such as tenderness at the catheter site, erythema, swelling, or purulent exudate at the entry site.

Next slide.

With respect to microbiologic inclusion criteria, patients will be considered to have catheter related bloodstream infection if they had concordant growth of the same organism -- I'm going to talk about the meaning of the wora "same" in a minute -- from peripheral blood and one of the following:

A blood culture drawn through the catheter with at least a three-to-one ratio on quantitative blood culture between the catheter blood culture and the peripheral blood culture;

Concordant growth of the same organism from peripheral blood in a catheter segment culture using either Maki technique with a cutoff of five CFU per segment or the Brun-Buisson technique using a cutoff of ten to the third CFU per segment;

Concordant growth with a catheter hub culture using a cutoff of ten to the third CFU per segment;

Concordant growth with a catheter entry site exudate culture or an infusate culture.

Next slide.

So what do I mean by concordance here?

We mean growth of the same species as shown by pulse field gel electrophoresis or an

antibiogram with PFGE recommended for common colonizers, such as coagulase negative Staphylococci.

The methodology used should allow characterization of different strains of the same organism, as well as contaminants, colonizers, and true pathogens.

Next slide.

Who would we propose excluding from these studies as not having the disease entity in question?

Patients with other endovascular infections, such as endocarditis; any patient with a prosthetic valve or vascular graft; patients with septic thrombophlebitis; or patients who do not have a vascular access device in place at the time of study entry; other bacteremic infections, for example, osteomyelitis; as well as patients who have received more than 24 hours of potentially effective therapy within 72 hours of study entry; those patients who could be treated with line removal alone; those patients who are moribund, who have renal or hepatic dysfunction except as provided for by the protocol; and those patients allergic to the study drug or comparator.

Next slide.

With respect to drug and dosing selection,

the study drug should be active in vitro against the pathogens of interest. The pharmacokinetics and pharmacodynamics of the study drug should be characterized and used as the basis for drug and dosing selection.

Because of the serious nature of bloodstream infections, bacteriocidal agents would be preferred.

The comparator or choice of comparators should be discussed in advance with the agency. The protocol should specify the duration of therapy in advance, and interactions with adjunctive therapy should also be considered.

Next slide.

One form of adjunctive therapy that should be specifically considered is line removal. Line change criteria should be specified in advance. To avoid or minimize introduction of bias, these should be applied uniformly within a given randomization stratum.

If a line is not removed at enrollment, subsequent removal should be considered evidence of treatment failure.

We would discourage line changes over a guidewire because of the potential for introduction of

infection of the new catheter. If such changes are performed, the criteria should be specified in advance, applied uniformly, and patients undergoing such guidewire changes should be the subject of an exploratory analysis to insure that bias has not been introduced.

Next slide.

With respect to the timing of assessments, at entry patients should have data obtained on vital signs, signs and symptoms of catheter related bloodstream infection, the type and site of catheter, and lab results.

Clinical and laboratory data speaking to other potential foci of infection should be obtained. Peripheral blood cultures and catheter drawn blood cultures should be obtained, and we would recommend two peripheral blood cultures.

And finally, if the catheter is removed, cultures of the catheter should be obtained of an exudate, of the hub, or infusate should be obtained.

After study entry, the first efficacy assessment would take place at **48** to **72** hours and would provide the first opportunity with respect to the clinical trial to determine if there was evidence of response to treatment or treatment failure.

End of therapy would be an optional visit at which the need for additional antimicrobial therapy would be decided on.

The test of cure visit would occur at least five days post therapy and perhaps longer for drugs with prolonged half-lives.

And finally. for patients infected with pathogens, such as Staph. aureus associated with metastatic sequelae, such as osteomyelitis, late follow-up should be obtained at least four weeks post therapy.

Next slide.

In terms of definitions of response, this will be defined as a composite endpoint with cure being established by all of the following:

Complete resolution of entry signs and symptoms:

Negative blood cultures at the test of cure visit;

And no late metastatic sequelae.

Patients will be considered to have failed treatment if any of the following occur:

Incomplete resolution of entry signs and symptoms;

Clinical deterioration or relapse

requiring a change in therapy-;

Need for line removal;

Persistent or relapsing bacteremia;

Death from infection;

Or late metastatic sequelae.

Next slide.

With respect to analysis of data from such trials, the major emphasis, as I've said, would be on those patients who have clinically, microbiologically documented catheter related bloodstream infections.

And as I've said, the primary endpoint will be a composite of clinical and microbiologic outcomes.

Secondaryendpoints could include separate clinical and microbiologic outcomes, time to clearance of bacteremia, development of resistance to study drug on therapy, and development of late metastatic sequelae.

Next slide.

With respect to which patient population should be analyzed, a modified intent to treat population should be analyzed consisting of all randomized patients who meet the clinical and microbiologic inclusion criteria at entry, that is, patients who have the disease entity at entry.

The protocol population would consist of those MITT patients who don't have any of the exclusion criteria, who receive study therapy for at least 48 hours, and also receive at least 80 percent of scheduled therapy, who do not have a change in therapy other than for failure, and how have all scheduled follow-up evaluations.

Next slide.

With respect to statistical considerations, studies will generally have an active control design since patients with this entity are generally treated at present.

If there is no comparator that is known to have demonstrable activity for this infection, then a superiority design would be appropriate.

If there is an approved comparator, which is not the case at present, or a well accepted standard of care, then an equivalence design might be appropriate if there is valid historical control data showing that the comparator has demonstrable treatment effect and giving a rigorous estimate of what that treatment effect is.

In addition, there would have to be a clinically acceptable delta between the control and test regimens.

Sponsors should also consider the implication of using stratified randomization versus subgroup analyses, looking at factors such as type of catheter, APACHE II score, and so on.

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I'd like to end here. I want to thank my colleagues on the working group and within the Office of Drug Evaluation IV for their hard work in constructing this proposed guidance, and I will stop here and I'll be happy to answer any questions from the committee.

CHAIRMAN CRAIG: The presentation is open up to questions.

I guess I can ask one. David, the European standard that was written did not include hubcap culture. Why are you including it?

DR. ROSS: I think the issue is really one of not overlooking a potential source of infection, and I think our perspective is that if one has a situation where you have a positive peripheral blood culture, but you have negative cultures of catheter, the catheter itself, then you don't have a direct demonstration in that case that the bloodstream infection arose from the catheter.

So the hub cultures are suggested in order

to not overlook that as a potential site of infection, and I think that the data suggest that that may, in fact, be a significant source of bloodstream infections, catheter related bloodstream infections. Sorry.

DR. RODVOLD: Dr. Archer.

DR. ARCHER: I'd like to emphasize that same point. I think the data that establishes the hub as the source of infection are like 15 years old and there's been like one study, decent study.

I think since then there's a lot more entry into catheters from multi-lumen devices where the hub contamination is probably higher than it was when those initial studies were done, and the chance for getting a single irrelevant contaminant peripheral culture and a contaminated hub is great.

So I think you can get those two positive and yet it not indicate a true catheter infection. I think without better data on the hub as a source it might be dangerous, and I would agree with that.

I have a second question. Where did the five CFU cutoff come from? I could find no reference for that versus 15.

Fifteen was the one established Maki.

DR. ROSS: I'm actually going to turn this

over to Dr. Fred Marsik, the microbiology reviewer on the working group.

DR. MARSIK: Yeah, I recognized that Dr. Maki had established the **15**, but there was also -- there is a reference where somebody looked at establishing five, and there is a reference in the guidance document to that effect.

DR. ARCHER: The reference just has no reference to five in that reference that you list.

DR. MARSIK: I'll give you a reference for that.

DR. ARCHER: I pulled the reference that you listed, and it doesn't have five in it.

DR. MARSIK: Okay. Well --

DR. ARCHER: It has 15, in fact.

DR. MARSIK: That was why I was wondering. The meta analysis paper, there is a reference for looking at five versus 15.

DR. ARCHER: It refers to that same paper, and it said 15.

DR. MARSIK: Right.

DR. ARCHER: So I don't -- the reason for that is I think that's a very, very low cutoff, and I think that, in fact, when you look at Maki's paper, **15** was a little questionable. When you get below that,

the incidence of contamination versus infection was real.

I think that needs to be looked at a lot more carefully.

DR. MARSIK: Certainly as specificity goes up, the higher the colony count. That's true.

CHAIRMAN CRAIG: Dr. Norden.

DR. NORDEN: David, that's a nice presentation.

DR. ROSS: Thank you.

DR. NORDEN: One of the questions I have, and **I** think it's going to be very difficult, is in the exclusion criteria line removal alone is sufficient. That's sort of an ex post factor determination most of the time.

I mean, if we pull the line and the patient gets better or if it, you know, coagulates negative staph. and we pull the line, we say, "Well, it doesn't need treatment."

DR. ROSS: Right.

DR. NORDEN: So how would you do that practically in a treatment protocol?

DR. ROSS: I think that is an extremely good question, and I think the practicalities of specifying criteria are going to be difficult,

especially when we recognize that for some catheter related bloodstream infections -- I'm thinking specifically of candida infections -- for a long time it was taught that all you needed to do was pull the catheter and not give any anti-fungal therapy.

And, in fact, we now know that you can have bad outcomes if you just pull the line.

I think that the best thing I could say at this point is that at this point it's something we don't have enough data to say which patients can be successfully treated with one removal alone. I think one hope that we have is that by stimulating interest in studying this as a separate entity, that that sort of data will become available, but I agree with you that is a very difficult question.

CHAIRMAN CRAIG: Dr. Chikami.

DR. CHIKAMI: I just wanted to follow up on Dr. Norden's point, and I think this may be something the committee may want to address during the general discussion, and that is the point that David raised.

The reason that this criteria was put in is because there studies are meant to be able to detect an antibiotic effective treatment, and somehow selecting those patients in whom you're likely to show

a treatment effect is really critical in terms of making the study design as most informative as possible.

So we'd be interested to hear what the committee thinks about this issue in their general discussion.

CHAIRMAN CRAIG: Dr. Reller.

DR. RELLER: A couple of points and questions about specifically the data you presented, David.

Even if there were a reference with less than five colony or more than five colony forming units, there's no microbiology laboratory in this country that I know of that uses that criterion. It's 15 or more.

And from a practical standpoint, those who culture at all, that's what's used, and I think that's what should be in the document the basis for which Dennis developed some years back.

The two questions are the clinical criteria very closely mimic those developed by the Critical Care Society for SIRS, systemic inflammatory response syndrome. Was there a reason or have I missed that they've changed? Why not make them exactly like those?

DR. ROSS: Well, we haven't given you the slide with the questions on it yet.

I think that you're referring to the fact that we make fever or I should say an alteration in temperature a required criterion, and in a sense weight that more heavily. I think that where that comes from is the feeling that usually the most frequent signal that causes people to obtain blood cultures looking for a catheter related bloodstream infection is fever.

Whether that should be a more important criterion based on the data available, I think, is very unclear, and I think that is an issue that we'd be very interested in getting the committee's thoughts on.

I think one of the things that we are concerned about, frankly, in terms of using the SIRS criteria alone is the fact that they are relatively nonspecific; that a large number of patients without infection could theoretically meet the SIRS criteria, and that's really the concern.

Whether it is scientifically justifiable, however, to give this additional weight to fever, I think, is a very real question, and that is, as you'll see, one of the questions on which we'd like to get

your guidance.

DR. RELLER: Right. I mean, I understand we'll come back to fever. I was simply not getting into the larger question of weighting, but why the listing of the components, that is, temperature alteration with one of the following.

The things that follow are virtually identical, but not identical to my understanding of the published SIRS criteria, and I mean, these are small points, but it's sort of like the five -- maybe larger points -- five colony units versus 15. I mean, the SIRS, I think, is greater than 90 on the heart rate, and a perhaps move objective, given the vagaries of observation of respiratory rate is to have the respiratory rate or the PA CO, less than 32.

It just seems to me a lot better to have any clinical criteria that are adopted match those that are clearly recognized and used. It would be as if one had an APACHE score with all components, except one of them was slightly different from the other components.

DR. ROSS: I understand.

CHAIRMAN CRAIG: Yes.

DR. ARCHER: For the test of cure, are you going to demand that blood cultures be drawn from all

patients who are clinically asymptomatic?

DR. ROSS: I'm beginning to think I don't need to put up the question slide. That is a question. I think that is an important question, and I think it gets down to what is the risk that we might miss in asymptomatic bacteremia, and certainly for other endovascular infections, and in particular I'm thinking of endocarditis here. We do get follow-up blood cultures.

So I think that's a question that we would like to get the committee's guidance on.

CHAIRMAN CRAIG: Dr. Parsonnet.

DR. PARSONNET: Also sort of in that line, are you going to have some criteria for when an echo will need to be done to rule out endocarditis?

DR. ROSS: The guidance does not go into that level of detail at present, as you know. I think that what we would rely on would be criteria, such as the Duke criteria in terms of establishing or attempting to exclude whether or not patients have evidence of endocarditis.

But I think one thing I want to emphasize is that given that this is -- the final document will be a guidance and will not be binding, that there's more than one way to satisfy the need to exclude such

patients, and I think that that would be, I think, another issue that we could address when we were revising the document.

But I think that we're welcome at this point to specify in great detail exactly what should be done because, again, this is a guidance. It's not intended to be a mandate.

CHAIRMAN CRAIG: Yes, Mel.

DR. WEINSTEIN: I had a little bit of a concern about the heart rate greater than 100 as well because a relatively large proportion of patients who have significant fever are going to have elevated heart rates. So you've going to wind up with a fairly liberal entry criterion if those are the two parameters.

CHAIRMAN CRAIG: Dr. Donowitz.

DR. DONOWITZ: One of the other issues is replacement of the catheter after you've pulled the infected catheter, if that's what it is. Guidewire you certainly brought up, but whether a catheter goes back the next day or it goes back five days later if somebody can hold off on that, certainly in my opinion affects the efficacy of therapy.

I don't find anywhere in here that that issue is addressed as to replacement of the catheter

at either site, by site or by timing and how that might affect the efficacy of therapy.

DR. ROSS: I think thinking in terms of catheter management is not so much to specify specific -- make specific requirements or recommendations, but more that studies be designed in such a way that it does not represent an entry point for bias; that criteria simply be specified in advance; and that they be applied uniformly.

So I appreciate what you're saying, but I think that is an issue that the sponsor should address, but I think the primary issue is is there a bias in terms of how the adjunctive treatment is being allocated.

CHAIRMAN CRAIG: Dr. Chesney.

DR. CHESNEY: I had four things I wanted to ask about.

DR. ROSS: Okay.

DR. CHESNEY: The first one, in defining a type of catheter, I wondered if you had thought about ventriculoatrial catheters.

DR. ROSS: No, we had not specifically discussed those. You mean, for example, for portal vein decompression.

DR. CHESNEY: CNS .

DR. ROSS: Oh, I'm sorry. No, we have not specifically discussed those, and I think that probably -- well, I think that there would be problems in that that might represent a very particular subset of patients who might have a different natural history, but we did not specifically discuss those.

DR. CHESNEY: The second thing, and this may be great for the general discussion, but it does apply to this, I notice that it says children will be considered when our experience expands. We have a tremendous experience, and I guess I would urge that when these criteria are developed that pediatric criteria are developed simultaneously, and the inclusion criteria would obviously be very different from children of different ages and so on.

The third thing is in response to Dr. Parsonnet's comment, not in response, but I noticed on page 10 of what we were given, which is exclusion criteria, it was patients with echo cardiographic evidence of endocarditis, and I think that raises a lot of questions in my mind, which is does that include a clot on the end of the catheter, which we see quite a bit in pediatrics. Does it mean that you have to do transesophageal echoes because that seems to becoming more of the gold standard?

So I just raise that for consideration, and I guess the fourth point was I wondered. I was interested to hear that these inclusion criteria are those of SIRS and adults, but they seem to me a little bit rigid, and I wondered about using categories, for example, white count between X and Y or blood pressure between or respiratory rate between X and Y.

It seemed you might exclude a patient whose white count was 11,900, which --

DR. ROSS: Right. No, one can imagine -- I mean, clinically if you have a patient with a white count of 6,000 who normally lives at a white count of 15,000, that could be a very significant increase. So I think that looking at the question of whether it changes from baseline is constructive.

CHAIRMAN CRAIG: Dr. Archer.

DR. ARCHER: The catheter site exudate culture, had you considered including Gram stain as a criterion for that as well? I could conceive of some ooze around the catheter which wasn't actually infection being cultured and skin contaminants being cultured as a result of that if just the culture were used.

DR. ROSS: Fred, do you want to?

DR. MARSIK: That's something that we had

thought about, and thank you for bringing that up. We can probably include that in the diagnosis. Thank you.

CHAIRMAN CRAIG: Dr. Norden.

DR. NORDEN: David, I wanted to question, and I'm not sure how the rest of the committee would feel about this, but I'm not sure that late metastatic sequelae really are a failure of treatment of catheter related infections.

And then it has real practical implications. I mean, frequently at least I have seen patients who develop osteomyelitis four, six weeks after the catheter has been removed. Treatment seems perfectly effective. The patient has become afebrile and responded.

It would also, if you don't have to look for this, if you're a sponsor, it makes your life infinitely easier if you don't need a six week or eight week follow-up, and I'm just not sure that that's a failure of treatment or that we know how to prevent late metastatic sequelae at all.

I think we ought to at least think about that as a possibility.

CHAIRMAN CRAIG: Dr. Chesney.

DR. CHESNEY: I would agree with Dr.

Norden because the seeding may- have taken place before the treatment actually began, and the treatment given for the catheter related infection may not treat the metastatic infection, which shows up later. But I agree. I wouldn't necessarily always see that as a failure of catheter.

CHAIRMAN CRAIG: Personally I think it's good to try and get control data, and so I would probably still keep it even though it might not mean much. It would be nice to get control data.

Dr. Murray.

DR. MURRAY: Yeah, I would tend to keep it as well because it should be the same in both groups. So that there may be more underlinement. It should show up in both groups.

CHAIRMAN CRAIG: Dr. Reller.

DR. RELLER: One of the concerns in the first place with developing criteria is that a drug could look great with catheter removal and only be head in the sand temporarily, and to get the follow-up and know what happens in equivalence in the treated and nontreated for the things that can't be prevented, I think, would be very, very important.

Andadditionally, the earlier discussions, and we'll have more, about how critical it is to keep

these patients stratified, delineated, defined as regards what's done with that catheter, the ones that are removed and not and by organism, this is a heterogeneous group of patients in response, and the intent is to find out what, if anything, a given antimicrobial adds to the therapy.

CHAIRMAN CRAIG: Okay. Thank you very much, David.

Now we run into the session for open presentations. We have two individuals. The first one is Ray Zhu from Biostatistics at Rhone-Poulenc Rorer.

DR. ZHU: Thank you.

Okay. Good morning. My name is Ray Zhu, Biostatistics Department in Rhode-Poulenc Rorer.

And first I'd like to congratulate FDA review team for putting together this well prepared draft guidance for treating important infections of catheter relatedbloodstream infection, and overall it carries some good, important points and provides helpful and practical guidance in planning clinical trial for this indication.

In my presentation, I'd like to discuss two issues related to clinical trial design.

Next slide, please.

And these two issues are one is the number of trials that would be needed for approval for this indication. Current guidance required two non-inferiority trial or one superiority trial.

And another issue is what is the appropriate delta, and this is discussed in this proposed guidance in the general sense principle, but not to a specific value.

Since recent, a lot of discussion in the regulatory agency around about what would be the appropriate delta to use in general antibiotics clinical trials, and there's a mindset shift away from the old point to consider rule where a wider delta can be allowed when response rate is slow, but a lot of questions ask can we make a narrower delta or make the delta selection independent of the response rate.

Since the delta selection and the number of trials jointly define the scale of clinical studies, so I think I will discuss the practical impact of this consideration. Keep it in the practical context because serious infection of catheter related bacteremia is very serious, and we only have minimal treatment options there, plus emergence of resistance may require more new antibiotics be put in the development line in the fast

pace.

Next slide, please.

I want to start with specifically for catheter related bacteremia a special case of ten percent delta with two non-inferiority trials, and based on our experience, when we do the sample size calculation, this will need 3,900 patients enrolled over about seven years. This is mainly because the enrollment rate is very low. Based on RPR's past experience 50 patients per month is the best. That is for a large multi-national trial, enroll patients from 180 sites, including 60 sites within U.S. and over across 12 countries.

And also, the large sample size is derived from low evaluability rate. Half of the patients may be excluded because either they don't have correct diagnosis or a lack of test of cure data.

And the success rate with standard practice is around 70 percent, which gives a high variability in outcome. It's also translated into high sampling variability on the study results, which requires large sample size to control it within a reasonable level.

Of course, this setting is not practical with its long development time, and the consequence

could be to limit patient access to new therapies and potentially also reduce number of drugs labeled.

Next slide, please.

Now, to balance the feasibility and the strength of evidence collected from well controlled clinical studies, so we asked this question if a single non-inferiority trial can be considered adequate if we have other data available.

This concept is described in FDA Modernization Act, and also with this division series of draft guidance issued since July '98 also support this concept by allowing single trial with supporting data.

Examples are hospital acquired pneumonia, sking (phonetic) skin structure infection, and UTI fever and neutropenia and meningitis.

So particularly for catheter related bacteremia, we're thinking maybe if we have approval for other serious infections or data from bacteremia secondary to other source of infection can be considered as supportive data, you know, to support with a single trial.

Next slide, please.

Okay. Now, to look at the delta and the impact of delta, I want to go through a specific

example, try to compare 20 percent delta, which is currently -- which is asked for from the old point to consider documents, and compare it against ten percent delta which has been discussed a lot recently, what should be the best to use.

Assuming here comparator has 70 percent success rate, and the sample size are corresponding to this two delta requirement is about 1,000 to 4,000 patients need to be enrolled. One is less than two years; another is over six years. So it's a four times increase.

Next, let's look at the potential benefits, again, by delta, 20 percent versus ten percent. If we have a 50 percent success rate for a treatment, that's considered to be not acceptable. With both of these delta, the chance of seeing it pass the equivalence hurdle is very low. It's both controlled by alpha value already in the design.

The difference lies in the case when a 60 percent response rate or success rate. So 20 percent delta would give some chance of letting that also pass even though it's not very likely, but it's still some chance, whereas ten percent delta will reduce that chance greatly. So that's the main difference.

But now the question is: is 60 percent

acceptable from a clinical perspective for this indication?

If that is the case, then ten percent delta might be overkill if we consider the practicality of two trials in this indication.

Of course, this delta decision has to be based on medical and regulatory considerations. It's not just a statistical issue.

Next slide.

The observation from the last slide mainly joined from this busy slide where the upper panel, I listed the corresponding costs in terms of number of patients needed to be enrolled and the time of the enrollment for different delta ranging from 20 percent, 15 percent, and ten percent. Also I gave one study and two studies per case.

And the lower part is the probability for a compound have a, you know, true response rate of 70 or lower. Seventy is assuming to be equivalent to the comparator, and the lower can be 65, 60, 55 and 50.

Here 50 is generally probably considered not quite acceptable, but the question is for those two highlighted rows, 60 percent response or 55 percent response, you can see even for FDA point to consider rule, the chance of passing 60 percent

response rate is not quite likely, but it's possible.

But if we give better, of course, give narrower delta, it will dramatically decrease that, but then again, this is the question: do we want to really control around that level?

So the conclusion from this slide is really delta 20 percent with two studies or 15 percent delta with potentially one study. It's really controlled the risk of letting a not quite effective drug, but actually still not that bad, like 60 percent response rate, reasonably controlled.

Next slide, please.

Another argument can support a wider delta around 70 percent response rate. It also has to do with varying the delta with the response rate. A wider delta of 20 percent rate can actually be justified as controlling alt. ratio, which is a composite risk combining burden due to success, loss of success, and burden due to increase in failure, and this is a widely used matrix for comparing two proportions, and also I think it's particularly relevant to infectious disease setting because failure may cause resistance.

And from this perspective, actually for 70 percent response, 20 percent drop on the response rate

is not adding too much burden comparing from 95 percent response dropping to 85 actually.

And this has been used in a point to consider and also is currently under discussion at the CPNP in Europe.

So this point combined with the risk control I discussed in the previous slides will support maybe considering wider delta for planning clinical trials.

Next slide, please.

So in summary, here is delta of 15 percent or wider can be considered acceptable for non-inferiority limit when success rate less than 90 percent, particularly for the case of catheter related bacteremia.

And the secondly is single, well controlled trial with supportive data can be considered adequate to meet regulatory requirement.

Thank you for your attention.

CHAIRMAN CRAIG: Any questions?

(No response.)

CHAIRMAN CRAIG: Thank you.

The next presentation is by Isaam Raad, M.D.

DR. RAAD: I would like to congratulate

the committee for the guidance. Having done research in this area --

CHAIRMAN CRAIG: Could you put the microphone on you? I think it's sitting there.

DR. RAAD: Sorry.

Let me start by introducing myself. I'm Isaam Raad with the M.D. Anderson Cancer Center, professor of medicine.

Having done research in this field over the last ten years without really having specific guidelines as to management and treatment, I think guidelines such as these would be extremely helpful in the future.

I want to make two points, one related to definitions and inclusion criteria. The guidance start with the premise of using specific -- I'm going to leave this till later -- with specific but flexible criteria, and in the introduction they speak of the fact that there would be inclusion criteria for suspected cases, but then availability would be determined on strict criteria of what is to be defined as catheter related bloodstream infections.

I think this is extremely useful. However, when it comes to inclusion criteria, we have relatively strict criteria which would serve as useful

criteria for evaluability, but not necessarily inclusion.

I'm pointing to the criteria on page 9, the microbiology criteria. I certainly agree that the cutoff point for a positive catheter culture should be more than 15 rather than five. I think the quantitative blood cultures should be greater than fivefold CVC versus peripheral. The three to one up to five to one might be too flexible.

But this would be useful as an evaluability criteria for definite cases, and inclusion criteria should be for suspected cases. A patient with a catheter with a likely organism, such as Staph. epidermidis, Staph. aureus or Candida parapsoriasis, no other apparently source, clinical manifestations of infection, such as cited here, and possibly catheter site inflammation, these would be the highly suspected cases.

And then later on when cultures are done, such as catheter cultures or quantitative lot cultures, these would be the definite cases for evaluation.

I want to mention something which is known to the advisory committee and to basically all of us here, that these are difficult infections to diagnose,

catheter related infections, and the usefulness of quantitative catheter cultures or semi-quantitative catheter cultures are limited in a sense based on our ability to extract organism from the catheter.

Studies by electromicroscopy by us, Casterton, and others show that these catheters are often colonized, but the catheter culture is negative even with the best techniques, such as sonication that would release organisms from the lumen and the external surface of the catheter.

I certainly agree with Dr. Gordon as to the cutoff point for more than 15, but also with others related to the hub cultures. The technique as to how you culture the hub is not well standardized.

And finally, on the culture of the infusate, I think just to mention a positive culture for the infusate plus a peripheral blood culture would imply catheter relatedbloodstream infection, I think, is too flexible. There needs to be some quantitation.

Dr. Maki uses more than ten to the two, and we've used the same. There should be some quantitation as to define infusion relatedbloodstream infection.

The second -- so I suggest that there would be inclusion of cases that are highly suspected,

probable cases, and also definite cases, and then an intent to treat analysis. There would be analysis of the probable and the definite cases, and then the evaluable and the evaluability as part of the subanalysis would analyze the definite cases based on quantitative catheter cultures and quantitative blood cultures.

I think it's important to take into consideration because of the fact in long term catheters or tunnel catheters or ports, that these catheters are often not removed, and especially in infections caused by Staph. epidermidis, to give consideration to some of the newer studies by Blotte and colleagues from France as to the differential to positivity time, and I think Dr. Mermel here has one study to support this presented viewing ICAAC, 1998.

The fact that the blood cultures would become positive at least two hours earlier if they're drawn simultaneous blood cultures from the CVC versus peripheral vein would highly suggest that the catheter is the source of infection. Quantitative blood cultures are not highly available, and this should be consideration.

There is a recent study by Blotte which is a prospective one published in September 27, 1999, in

the Lancet, which would be useful to this draft guidance.

Finally, the second issue is related to blood cultures in terms of evaluating should they be required in all patients at the test of cure **and** follow-up visits.

Now, this is not endocarditis here being looked at. This is a transient bacteremia that would include Staph. epidermidis as one of the organisms.

And if the patient is now discharged, is doing well, comes back seven days later, seven to 14 days later for a test of cure, in the absence of fever or clinical manifestations of infection, what is the meaningful -- how meaningful is a positive blood culture from this patient?

For Staph. epidermidis we know that in a patient such as this one the positive predictive value of a positive blood culture is extremely low. Bates and Lee, for any positive blood culture in the absence of fever or chills in JAMA, 1992, showed that the probability of a positive blood culture is 1.5 percent. This would reflect through bacteremia.

There are other studies for, for example, Staph. epidermidis, again, positive predictive values extremely, extremely low.

Even by a more recent study in the Clinical Infectious Disease, 1996, where they looked a febrile patients with a positive or negative Staph. blood culture and determined the positive predictive value, in these febrile patients the positive predictive value of a positive blood culture for Gram negative Staph. is 26 percent.

So if we get a patient who is afebrile and have a positive blood culture, what does that mean in the absence of clinical manifestations of infection, and why should we do it?

I would do it if the patient -- and then most investigators will not perform it. I'm not sure if the IRB would approve it because of its lack of usefulness and we're drawing blood on a patient in the absence of a clinical indication.

So what I would suggest is that these blood cultures should be done in a febrile patient or patients with the signs of infection at the catheter site if the catheter has not been removed, such as a tunneled catheter or a portion, or patients with Staph. aureus versus Staph. epidermidis.

Staph. aureus bacteremias in patients who are not able to mount a febrile or manifest with fever, such as patients on high dose steroids or

patients with renal failure.

Just a quick word about renal failure. I noticed that one of the exclusion criteria suggested in the guidance is to exclude patients who have renal or hepatic dysfunction from these studies, and I find no reason for this. Hemodialysis patients get catheter infections and should be included, part of the evaluation.

So the two points I'm making is to include patients with probable catheter related bloodstream infections. Then do quantitative catheter cultures and quantitative blood cultures. Consider differentialpositivitytime, and then evaluate intend to treat all patients with probable infections included and then concentrate in a subanalysis on the definitive cases.

And the second point I'm making here, that the blood cultures should be done as a test of cure in patients who are coming back with fever or any of the signs suggested here to suggest a recurrence of infection.

Thank you.

CHAIRMAN CRAIG: Any questions?

Dr. Murray?

DR. MURRAY: Sure, Sam, as long as you're

up there.

Taking Staph. epi. for example, and of course, the patient population you're dealing with is a little bit different from what may be out there, I mean, that's one of the ones I think people are going to have trouble with. Is removing the catheter sufficient, et cetera?

How would you approach Staph. epi. in terms of setting up a trial? Length of therapy; just taking out the catheter and not treating; three days, five days, ten days, 14 days? Just for curiosity, how do you view that even in your population?

DR. RAAD: Yes. I think reviewing the literature, in our population and others most of what is there in the literature would suggest that Staph. epi. you can treat without removal of the catheter, but this is clinically most applicable in patients with a long term tunnel catheter or port.

DR. MURRAY: Actually I meant in the other population where it's a peripheral, where it's a type of catheter that you would just remove, not in the ones that you want to keep in, but in the ones that are short lines, that are very easy to remove, and have been removed because the patient was febrile and the physician at the time of seeing the patient

removed catheter.

The treatment of those patients who have had the catheter removed, as opposed to --

DR. RAAD: Oh, how long you ask. I don't think this is defined, and I think this is why the guidance is helpful. We're going into an era where we're starting to see prospective randomized studies dealing with catheter related bloodstream infections.

All that we have is retrospective data and more anecdotal data. So it's not well defined. In one studypublishedin Infection Control Epidemiology, these were treated whether removed or not removed. The catheter related Staph. epidermidis bacteremias required two positive blood cultures, were treated with five to seven days, and did reasonably well.

So the question is: do you need to treat them if you remove the catheter? This is yet to be answered.

I think the problem in the literature is many of the cases labeled as Staph. epi. bacteremias might not be true bacteremias, might be a positive blood culture drawn through the CVC which would reflect an interlumenal colonization or hub colonization. So this is why it's important to have at least one concurrent peripheral blood culture.

CHAIRMAN CRAIG: Dr. Mermel, just for the record, Dr. Len Mermel joined the group. He's from Brown University, and a consultant to the committee.

FDA Representative

DR. MERMEL: Sam, just a couple of quick questions.

Would you also consider the repeat cultures with Candida as you, you know, mentioned with Staph. aureus? Would you put Candida up there in the same category?

DR. RAAD: Yes. I would consider Staph. Aureus and Candida versus Staph. epidermidis and some of the other skin organisms.

DR. MERMEL: Yeah, and then with the infusion related cutoffs, I know that Dennis and you and others have used the same cutoffs, but I don't think really it's undergone any rigor with regards to, you know, what we should really use for a cutoff.

I mean, if you saw a funny Gram negative and it was ten colonies per mL in infusate and someone had, you know, a percutaneously drawn blood culture of the same organism and there was no other obvious source based on, you know, a thorough exam --

DR. RAAD: The reason why I say there needs to be some quantitation is my concern is with

Staph. epi.

DR. **MERMEL:** Yeah.

DR. RAAD: We have finished a study, a prospective study on more than 500 patients and cultured basically the infusate from all of these patients, and we get often -- this is more of contamination of the Staph. epi. -- ten colonies or 15 colonies from the infusate per mL, and these patients were afebrile, have no evidence of infection, but sometimes you might have a concurrent bacteremia, and then just to make sure.

So for Staph. epi. at least there needs to be some cutoff point.

DR. MERMEL: Obviously what you're getting at is the predictive value was different as I think Armstrong had shown ten years ago looking at quantitation of skin organisms at the insertion site of the Staph. epi. They had a much higher cutoff. Yet Staph. aureus and some other more pathogenic organisms had a lower -- I think any at the insertion site appeared to correlate with catheter related bloodstream infections.

So maybe we need to vary the definition based on, you know, Staph. epi. and others.

DR. RAAD: It might be. I'm also talking

about skin that they exudate. I agree with doing a Gram stain for the exudate because, again, some discharge from the insertion site might not mean parallels, and this has to be.

DR. MERMEL: One last point. Barbara's comment. We had a consensus panel last year that I was involved with in Spain and talking about coag. negative Staph. short term cath. related infections, and some of our infectious disease colleagues in the Netherlands said most of the practice at least in their country was with coag. negative Staph. bacteremia. They don't routinely treat unless, you know, the patient is feverous, continues for days, you know, after they have removed the device, seemed to be, you know, the antithesis of what we seem to do here in the U.S.

DR. MURRAY: Well, certainly when some of us were in training, a few years before you, we didn't treat them either once the catheter came out, and that's sort of something that has evolved without particular data to support it.

DR. ROSS: Thank you.

Just a point of clarification. I just want to say we absolutely agree with Dr. Raad that patients with renal failure should not be excluded

routinely from these studies, and we may need to rephrase the way that's written in the guidance.

The intent is that the protocol specifically address such patients, not that they be excluded, but we certainly recognize that these are patients who are at high risk for catheter related bloodstream infections not only because of hemodialysis, but because of other medical interventions which may be needed.

CHAIRMAN CRAIG: But they also involve patients who's going to have an alteration in the pharmacokinetics of the drug, and so that could also cloud the picture. So you wouldn't just want to do the study in those patients.

DR. ARCHER: Excuse me. Dr. Raad, one question. Would you support a trial where it's documented coag. negative Staph. bacteremia; the catheter comes out; where one of the control groups is no therapy at all? Not that any company would ever do that.

DR. RAAD: Yes, I would, and I think, again, but these should exclude neutropenic patients. I think in neutropenic patients there is some mortality if this is true Staph. epi. infection. In neutropenic patients there is a 12 percent mortality.

so I don't think these should be treated. Otherwise I would support it.

DR. MERMEL: Wouldn't you also exclude patients with prosthetic valves as well?

DR. RAAD: Certainly.

DR. MERMEL: Obviously.

CHAIRMAN CRAIG: Okay. Dr. Reller.

DR. RELLER: I have a couple of questions for Drs. Raad and Mermel.

You urged that if infusate and hub cultures were included in the criteria, that quantitation be used. Recognizing that culturing skin and hub and infusate may be important in studies trying to delineate where all of this starts, but in a clinical trial for the target patients that we are talking about, what role -- what do you do with infusate cultures, hub cultures? What information does one gain that could not be obtained by peripheral blood cultures or Maki method cultures of removed catheters?

DR. RAAD: Do you want to? Go ahead.

DR. MERMEL: I think Sam and I would probably both agree that there are certainly a number of articles in the published literature where Dr. Maki's -- you know, the roll plate method, that people

have had catheter related bloodstream infection when they found positive infusates, for example, or Tony Stiges-Serra obviously has a number of studies, as do others, where they found the hubs revealed pathogens that weren't revealed simply by rolling the catheter.

And then Sam has, you know, championed the cause and Barry Farr (phonetic) had a recent meta analysis, as you know, in Journal of Clinical Micro., using possibly quantitative methods which are not, as you know, routinely used in the vast majority of U.S. microbiology laboratories because of their labor intensiveness.

They have much higher sensitivity, and maybe with those methods we could get a higher yield from intraluminal pathogens as well as extraluminal pathogens. So it's possible if something like sonication of the catheter was used. We might not miss some of the organisms where we were using the roll plate method to help define catheter related bloodstream infection with concordance with the percutaneously drawn blood culture.

So I think, you know, there are studies where those -- I think your point is very well taken, but I think looking at Barry Farr's meta analysis, the sensitivity of the methodology for the roll plate

method is suboptimal in some conditions, and maybe in those conditions, particularly intraluminal infections, might have a higher yield.

Sam?

DR. RAAD: Yes. I think the roll plate method was an initial first step, but even in Maki's studies and later studies by us and others, the sensitivity of this method is 45 percent being the highest.

The reason is that the roll plate method cultures the external surface of the catheter only, and there is no attempt to release organisms that might be imbedded in biofilm.

The sonication method might be better because you get organisms from the external surface and the internal surface, and you release organisms that are sessile or imbedded in biofilm.

Again, this is not the perfect method, sonication being sonication.

The question: if you do sonication, and I think what you're raising is the validity or need if you do a biluminal kind of a catheter culture technique, which is quantitative, do we really need to do a hub culture or an infusion culture of the infusate?

This is unknown, but theoretically you can imagine that there might be colonies in the hub or might be colonies going through the infusate and not sticking to the lumen of the catheter and causing catheter related bloodstream infections.

For the infusate, this is going to be transient, but nonetheless, this would be meaningful, if done, could be meaningful to show that there is a catheter related bloodstream infection, but you probably need a DNA typing in this setting to make sure that the same organism from the infusate or the hub versus the peripheral vein.

DR. MERMEL: On the other hand, let me say I would be satisfied, I mean, if there were a study done.

When Sam and I do studies, and we have done things, our own studies, we've utilized more than one method. If I utilize the roll plate method, I use another microbiological method when we do studies on say preventing catheter infections. So we try to obviously catch as much as we can, although the questions are somewhat different as you've raised.

I think if a sonification method were used, for example, myself, my personal opinion, I wouldn't feel compelled that those other cultures

would have to be done as long as all of the labs were doing, you know, that same method

DR. RELLER: My concern is trying to make these thing -- I mean, there are reasons to look at them, and it seems to me if you have an infusate that's positive and nothing else is positive, it's an infusate related infection, not a catheter related infection.

And what's the target that we're after? Clinically we're after patients who have documented -- and we'll get into further discussion there, what it takes to be comfortable with documentation -- documentation of that they're sick and they've got bacteremia, bloodstream infection, bloodstream and infection, sick and with positive blood cultures, and then how to treat it.

And it seems to me that, you know, trying to delineate how sensitive and specific all of this, in quotes, peripheral stuff is misses the mark of what we're really after, given the documented ambiguities, the lack of standardization, and so on.

And this is going to be tough enough to study anyway, but if we start having a mixed group of patients coming into it, it even makes the job more difficult as opposed to saying some day down the line,

when people work out all of the quantitative relationships between hub and this, that, and the other, then we can consider it, but right now I'm very uncomfortable with hubs and infusates at helping us get at the central clinical issue that we're attempting to address.

DR. MERMEL: The problem is, as you've probably seen clinically, there are those patients that seem to have compelling evidence of a catheter related bloodstream infection, and a roll plate technique alone is negative, and yet there's no other source, say, of let's **say** a coag. negative Staph. or a Staph. aureus bloodstream infection.

So that's okay if you just use the roll plate, but realizing that you're going to miss a large number of patients, you know, based on your microbiological criteria.

DR. RELLER: I mean, there are those who don't think the roll plate is helpful in this in the first place because you've already got done one of the prime and stratified characteristics in the therapy of these infections.

So that what it comes down to is if we're considering these other things that are not standardized yet, because the roll plate, semi-

quantitative roll plate methods is not perfectly sensitive for all of the two reasons that Dr. Raad has mentioned, with the electron microscopy biofilm, and so on, then it puts even more emphasis on what may be central in the first place, namely, the documentation of bacteremia with no other source recognized, which is part of the definition, and either the catheter is thought to be the cause and is left in where you wouldn't have the roll plate anyway, and you give therapy and the patients do or don't respond.

And most of these are going to be coagulase negative Staphylococcus, and if there's no other site and the patient gets better and the follow-up cultures, if we decide that that's important, are negative and there's no hardware in place anyplace, I mean, I think most people clinically would accept that if the bacteremia is with Staph. epidermidis and the catheter is the only plausible culprit, it's real.

CHAIRMAN CRAIG: Yes, Dr. Archer.

DR. ARCHER: One more.

CHAIRMAN CRAIG: This is a question or is this --

DR. ARCHER: Well, a question and a comment.

CHAIRMAN CRAIG: -- part of the

discussion? Because we're going to have discussion in a little while.

DR. ARCHER: Right. Just kind of a comment. It's just that there's so much lack of knowledge it seems to me this is the perfect opportunity to answer a lot of these questions by doing comparative trials with different agents and using fairly broad criteria, specific criteria, with one of the outcomes being to assess which of these methods really does predict outcome.

And so I think this is a chance to really get some information we don't have. I think we should be thinking about that when we're thinking about criteria and design of studies, not only setting up the trials that differences between drugs, but gain some information on how to make a diagnosis and how to assess outcomes.

CHAIRMAN CRAIG: Any other questions or comments right now?

(No response.)

CHAIRMAN CRAIG: We'll take our break, and we'll be back at ten o'clock.

(Whereupon, the foregoing matter went off the record at 9:42 a.m. and went back on the record at 10:03 a.m.)

CHAIRMAN CRAIG: Okay. Gary, are you or David going to introduce the questions?

DR. CHIKAMI: David will.

Before the specific questions go up, I just want to say I appreciated -- we all appreciated -- the wide ranging discussion that occurred this morning and sort of look forward to more of that.

And the questions that we posed are meant just to focus on a couple of specific areas that we want the committee's comment on, but I think we would appreciate the committee's comments on any aspects of the guidance as it related to the document.

CHAIRMAN CRAIG: Yeah, I have a lot of things listed down that we'll go through in addition to the questions.

DR. ROSS: Okay. With respect to the definition that is given in the draft guidance for the study population, is the weight given to fever as a clinical inclusion criterion scientifically appropriate?

If not, how could the clinical inclusion criteria be designed to insure diagnostic specificity?

In addition, in which situations would an identical antibiogram suffice to demonstrate concordance between peripheral blood cultures and

either catheter drawn blood cultures or cultures of catheter hardware, and in which situations would pulse field gel electrophoresis be needed?

Going to the issue of assessing efficacy, given that both clinical and microbiologic criteria are important in defining the study population in determining outcome, how shouldmicrobiologic outcomes be assessed?

CHAIRMAN CRAIG: Thank you, David.

We'll start off then with the first part of the first question about the weight given to fever as a clinical inclusion criterion, scientifically appropriate.

And I guess I'll start by first asking our consultant, Dr. Mermel, whether he would comment on that question.

DR. MERMEL: Thanks, Bill.

CHAIRMAN CRAIG: I always get the antibiotic questions. You get these.

DR. MERMEL: Yeah. I think it's a difficult question to answer. As Dr. Archer pointed out, we still have so much more to learn with regards to appropriately studying these sorts of infections.

I think it is given appropriate weight, realizing that from studies down now, I think, 20

years ago, there's a potential for the elderly, for example, 15 percent or so, to have bloodstream infection without a febrile response.

On the other hand, if we're going to look at putting a new product on the market to treat infections, I think we all would like to have some sense of the seriousness of it, and if we're going to treat people who don't have a fever and then look at efficacy of a drug, I have some problems with that.

So I think, my personal opinion, but again, I think scientific rigor is a little bit shaky. Realizing that we may miss some populations, people on steroids, the elderly, who may not mount much of a febrile response, despite that potential weakness, I think it's fair to give it the weight it's given.

CHAIRMAN CRAIG: Any other comments from anybody else? Dr. Chesney.

DR. CHESNEY: I'd just like to reiterate how strongly I think some of us feel that the pediatric studies should be done simultaneously, and certainly neonates and specificallyprematures usually don't have fever with Staph. epidermidis sepsis. So I'd just like to add that.

CHAIRMAN CRAIG: But are you saying that you would want to change the criteria or we would just

not include those in the studies?

DR. CHESNEY: I'd like to create a whole separate set of criteria for children. I think they have to be separate.

The other issue that was mentioned to me just a few minutes ago is that it can be difficult to get peripheral cultures on prematures. So maybe you would require two central line cultures. I mean that whole issue, I think, would need to be discussed and a separate set of inclusion criteria.

CHAIRMAN CRAIG: Dr. Danner.

DR. DANNER: I think that the criteria giving weight to fever is, in fact, appropriate. In terms of pediatrics, obviously the guidelines would have to be a separate set for adults versus children, even you know the things like the blood pressure criteria and the heat rate criteria. Newborns have heart rates over **100** when they're normal. So these things would have to be redone and made specific for children.

In terms of -- which I think is on the same topic -- in terms of the issue of not following the SIRS criteria closely, I think that's actually appropriate. It looks like the changes in the criteria have, if anything, set the bar a little

higher, and the SIRS criteria as a gold standard have been a terrible gold standard. They have been selected for a patient population that is particularly homogeneous or that responds similarly to a variety of interventions, and I think within critical care medicine there's widespread dissatisfaction with the criteria as they exist.

So I think setting the bar a little higher for entry in a specific type of infection, like catheter related infection, is in fact the right way to go with these things.

CHAIRMAN CRAIG: Dr. Archer.

DR. ARCHER: You kind of have to ask yourself why would anybody be getting a blood culture in a patient who's not febrile, and the things that come to mind would be patients are not doing well, and that tends to be sometimes when patients aren't doing well for whatever reason, blood cultures are drawn, and I think the chance for contamination and inappropriate attributing positive cultures to whatever the patient's clinical condition is is a lot higher when you don't have something like fever.

CHAIRMAN CRAIG: I agree.

Barth, did you have your hand up?

DR. RELLER: I just wanted to ask Bob. Is

there an imminent prospect of the SIRS criteria being revised?

DR. DANNER: No is the answer to that, but it's not because people like them the way they are. It's because people don't know what to do with them.

CHAIRMAN CRAIG: Yes, Dr. Donowitz.

DR. DONOWITZ: Dr. Chesney spoke to this, but, again, representing the pediatric side of things, I think it is possible to include pediatrics in this general study if you delete the neonates and the premature neonates. Unfortunately that deletes a huge population where we see catheter related infections. It would be a very large study group which would be nice to have data in.

And so I see that almost as a separate entity, but I think if you took intensive care unit patients, trauma patients, oncology patients, we could probably go with the same criterion in the group above the premature neonate. The premature neonate very rarely mounts a fever with infection and oftentimes becomes hypothermic, and so there are so many of these criteria that really would not apply.

But with the older kids, I don't know how you feel, Joan, but I think it could well be used to include our older patients.

CHAIRMAN CRAIG: Dr. Chesney.

DR. CHESNEY: A couple of things along that line.

I think in pediatrics we put a fair bit of weight on where the temperature is taken. So we'd have to specify whether it was axillary or rectal because an axillary temperature of 37.5 is really a rectal temperature of 38.1 or 38.2.

I'm also working at St. Jude now, and I know that they work up a 37.8 rectal temperature as fever. so that's just a sort of oncologic, immunocompromised group that might have different criteria.

CHAIRMAN CRAIG: Any other comments on that particular questions?

I'm sort of getting the feel from what has been said that everyone feels that the criterion putting the extra emphasis on fever is appropriate. Everyone is sort of shaking their heads over this way, too. So I think we've answered that first question, that the committee does feel that that's appropriate.

I think the one little tidbit that was there was that clearly in some patient populations, they are going to be excluded.

I would probably add renal failure

populations to the group as well because they frequently don't mount as much of a fever as well, but with that understanding at least for getting the drug approved for this indication, the committee does feel that fever is indicated.

Julie.

DR. PARSONNET: Just one quick comment to echo what was just said, that the site of temperature also is important in adults, and people are using all different methods now, and that should be stated pretty clearly.

CHAIRMAN CRAIG: Yes, Dr. Murray.

DR. MURRAY: Yeah, I just wanted to possibly extend just a tiny bit on what Gordon said because I think you were saying this, but if you do have positive blood cultures drawn because someone had failure to thrive and this as written would exclude them from being studied, but that would be a population you'd be interested in, obviously you'd want to have to repeat the blood cultures at the time of entry. So by then you'd have two or three or four known positives to continue inclusion, and you might have to have stricter microbiology criteria, but that would be an appropriate population to study, I think.

CHAIRMAN CRAIG: Go ahead, Gordon.

DR. ARCHER: Just that one comment about how the temperature is taken. Some hospitals have gone to very nontraditional ways of measuring fever. Unbeknownst to us, for instance, our hospital goes to this thing where you rub something across the patient's forehead and then stick it behind their ear, which is as far as I can tell a fairly nonstandardized way of taking temperatures, and some use the ear.

And I **100** percent agree with you. I mean you really have to know how the temperatures are being taken and how relevant those temperatures. That should be standardized.

CHAIRMAN CRAIG: At least I know at least from some of the workbooks I've seen from some of the pharmaceutical companies when they're asking you for fever, they have down all of the choices that can be done and there are quite a few of them.

Any other comments on that specific question?

(No response.)

CHAIRMAN CRAIG: Okay. Let's move on then. I guess we've added the second part, too.

Is there anything -- let's just see if there is anything additional besides fever that people feel need to be added to enhance the diagnostic

specificity. Yes?

DR. CHRISTIE-SAMUELS: I have a question. I wondered if you couldn't mix and match the systemic and the localized signs of infection. As they're written it says "or," I wonder if we couldn't have "and/or" for the clinical inclusion criteria.

DR. ROSS: I think the way the guidance is constructed right now, if you had an afebrile patient who, for example, simply had a tender erythematous area over the catheter and had microbiologic evidence of catheter related bloodstream infection, that even if there were no systemic clinical signs of infection, that patient will be considered to have a catheter related bloodstream infection.

For both purposes of the guidance and I would also say from a clinical standpoint, I think most clinicians would consider that patient to have bloodstream infection arising from the catheter.

CHAIRMANCRAIG: Any suggestions, anything that we could add to the clinical criteria that would be helpful?

Dr. Reller.

DR. RELLER: Respecting Bob Danner's comments, I mean one could put down as an alternative option for the respiratory rate greater than 20 the

fall in arterial PCO_2. Do you think that's reasonable, Bob?

I mean the way the SIRS have it where it's rapid respiratory rate or fall in PCO,.

DR. DANNER: I think that would be fine. I just think that in terms of developing the criteria, that particularly early on in this one in doing studies, what you want to do is to try to select as specific a population as possible that really does have catheter related infection, and you don't want a lot of noise from patients who don't have that and are in here.

So that's why I think the fever thing is important in terms of, you know, looking at -- you know, adding PCO, in or something like that, I'm not sure if that -- I don't that, just off the cuff, I don't think that would make your patient selection less specific. So I guess I think that would be okay.

CHAIRMAN CRAIG: Dr. Murray.

DR. MURRAY: Well, just that I think a respiratory rate of greater than 20 is pretty nonspecific. So I think Barth was trying to look for a way to maybe make that better, not that this was --

DR. DANNER: Yeah, individually, all of the criteria are nonspecific. I mean that's one of

the real problems, and they really have to be looked upon as a whole and hopefully will acting as a whole select a fairly -- a reasonably specific group of people who really do have the disease.

CHAIRMAN CRAIG: But at least I got the impression, Barth, that you were trying to expand it so that there might be somebody that didn't have a high enough heart -- respiratory rate, but did have lower PCO_2s. Am I --

DR. RELLER: No, this was just another perhaps more objective measurement of tachypnea. I mean, let's face it. Some of these observations of how fast people breathe a minute are pretty -- I mean they may be observed or they might not be observed accurately or counted accurately.

And I think that was one of the reasons in the **SIRS** that the fall in PCO, is a more objective measurement of tachypnea, in a way was there.

Even in the aggregate, the SIRS criteria, **I** mean, something's going on and there's altered physiology. The patient is sick, and because of that lack of specificity individually or in the aggregate, that's what makes the microbiology criteria in this indication so crucial.

And I don't want to get hung up on the

SIRS. It's just that it just seems to me that, you know, they are what they are, a nonspecific indicator of altered physiology, which is what we want. We want somebody who either has local objective evidence of infection, either objective, localized evidence of infection with positive blood cultures or they're sick with positive blood cultures, sick in the way that implies the possibility of infection with SIRS, and I think that's fine.

DR. DANNER: I mean, I guess, you know, just to illustrate a place where maybe the PCO, won't be all that helpful is that for the SIRS criteria they're defining a group of people that are generally critically ill or are in ICUs or are heading there, and a lot of those people are having blood gases drawn for a variety of reasons.

In this population where you're selecting for catheter related infection, in the vast majority of these patients there's no reason to get a blood gas, and if somebody is not tachypneic and they don't have these other problems or respiratory problems, why would you get a blood gas and even know the PCO,?

DR. RELLER: Maybe I have the wrong emphasis. I wasn't suggesting that we need to add it because of its intrinsic value, but simply in the SIRS

it's listed as an "or" so that if somebody at the time of enrollment happened to have a PCO, that was low, in addition to fever, and they didn't have these other things, that it wouldn't, you know, exclude them.

But the way it's written, it's rapid respiratory rate or an alternative surrogate for that. I mean I'm not trying to make a lot of that.

DR. DANNER: As long as people aren't drawing blood cultures to try to get somebody to meet the criteria to get into the study. I mean that's a silly use of blood gasses to get a number.

CHAIRMAN CRAIG: Okay. Anything else?

(No response.)

CHAIRMAN CRAIG: I guess we'll move on then. Our next question is in which situations would identical antibiograms suffice to demonstrate concordance and in which would pulse field gel electrophoresis be needed?

Again, I'll start with Len. Dr. Mermel.

DR. MERMEL: I think and I hope Dr. Raad there would agree and come up if he has some differences of opinion. I think most of us that do studies have required pulse field gel as kind of our gold standard in looking particularly at pathogenesis of catheter related infections.

However, I think most of us would agree that outside of the coagulase negative Staphylococci, I mean, if you have Staph. aureus in a catheter tip and Staph. aureus in a percutaneously drawn blood culture, and particularly if they're the same antibiogram or Kleb. pneumo. or whatever the pathogen is, I think other than coag. negative Staph., I don't think we need pulse field gel for other organisms, number one.

So I would say certainly we don't need molecular fingerprinting for other microbes other than the possibility of coag. negative Staph.

And in coming back to coag. negative Staph., thinking about -- and this goes back to also some earlier comments with hub cultures and infusate cultures. Most of the studies in the literature because there's nothing that I'm aware of prospective looking at therapy for device related infections, in most of the studies we're only answering questions of pathogenesis, and since many of these infections are caused by coag. negative Staph., we've used pulse field gel, Dr. Raad, myself, and many others, to tease apart where these organisms are coming from.

But we're not asking those sorts of questions here. So one might also ask if you find

coag. negative Staph., significant growth, on a cath. tip and a percutaneously drawn blood culture and now with a little more data coming out that you can even have multiple strains causing a bloodstream infection, do we need, knowing that many institutions won't have this available, the rigors of pulse field gel to answer the question as to whether or not a therapeutic agent is efficacious?

And I'm not so sure we do in this purview as compared to looking at pathogenesis, in other words, looking at using the technology to answer questions. Are the organisms coming from the skin or the hub or the infusate? Here we just want to know is it real and is the drug effective.

And I think even with coag. negative Staph., if we felt that the patient met these criteria, although I've been a strong advocate of molecular fingerprinting, it may be less relevant even with coag. negative Staph. in this scenario looking at treatment rather than pathogenesis.

CHAIRMAN CRAIG: But wouldn't you think that it would be better to at least get data on that question and by that, requiring the pulse field gel electrophoresis at least for the first few studies that start coming by so that then if one finds that

it's not necessary then one could later reduce it instead of essentially throwing it up and not having any -- having it be data driven?

DR. MERMEL: I mean, again, you're preaching to the converted in terms of the beauty and importance of the molecular fingerprinting, but again, we've really applied it to -- I'm just trying to think as a pragmatist, and we have applied it so much for pathogenesis. If we can do pulse field gel, I think that would be ideal. That would be a gold standard, and I push that, you know, in my own publications looking at studies of pathogenesis.

But I'm not so certain we have to in this setting. Some other nuances, again, it also depends on your microbiological methods. Are people picking all of the colonies and then subjecting those to pulse field gel?

There are a lot of nuances as we've raised the bar with regards to the rigor of molecular fingerprinting. We have to go back to the basics of how are people picking the colonies. Are they sitting out at room temperature for three days? Are we picking different colony counts? Are we running the gels on those?

There is, I think, some recent debate as

to -- and people have raised the question as to -- again, having different strains causing a bloodstream infection. So if you use pulse field gel and you lack some of those kind of simple lab bench maneuvers to make sure you were actually running the gel on all of the different possible colonies or strains that might be causing infection, you might call something not being catheter related, whereas indeed it is.

CHAIRMAN CRAIG: Dr. Murray.

DR. MURRAY: Yeah. I think just for the reasons you've stated that is why you need pulse field for Staph. epi. You're willing to not do it for Staph. aureus because you're more convinced it's the real cause of the bacteremia and the fever syndrome, and you're not as sure about the Staph. epi., which is why you're even questioning doing the -- why you do the pulse field in your studies.

And I think that's the very reason you need it, and I'm willing to lose some patients that you don't pick the right isolate for a study purpose because I'm not even convinced that in the patient where the catheter comes out that you actually need therapy for Staph. epi.

So I think you need to raise the bar. Keep it as high as you can for this particular

organism.

CHAIRMAN CRAIG: Dr. Archer.

DR. ARCHER: I think this gets back to another issue that Dr. Reller and I were talking about at the break, and that is what we're trying to define here is catheter related bacteremia, and I'm concerned that the bacteremia part is not being well defined, that is, on the basis of these criteria a single blood culture could be linked with a catheter culture, a nonblood culture, and that would be considered catheter related bacteremia.

I'm concerned that you need at least two blood cultures in order to diagnose bacteremia, and if you have two blood cultures, say, one from the catheter and one peripheral, then a pulse field gel, I think, would be very helpful because those should be clones. They're taken at the same time from the same patient, and if they have a different pulse field pattern, then they're different bugs, and they're not the cause of bacteremia.

So I think in that case establishing that both of those came from the same blood, they're both from blood in the patient at the same time would be helpful.

I agree when you're trying to take

separate colonies from a catheter which might have different pulse field characteristics, one of which might have been the cause of bacteremia, you might get a difference, and yet that still might not rule out the catheter as the cause of bacteremia.

So I think that's a different question, but I think it's really important to establish bacteremia first, then the catheter as the source of the bacteremia second.

CHAIRMAN CRAIG: Dr. Danner.

DR. DANNER: The Critical Care Medicine Department at NIH oversees the placement of vascular access in the clinical center, and in that role, we either place or oversee the placement of 1,500 catheters a year, and we monitor those catheter placements for infection and for complications.

It is our experience that pulse field, in fact, does seem to us to be very necessary because even when you have four different isolates or four isolates of Staph. epi. in a given patient, you may have four completely different organisms by pulse field.

And so I think for that specific organism, pulse field probably is necessary because otherwise you just have no idea of whether you're really looking

at a catheter related infection or not.

You know, I think, again, at this phase we want to be specific. We want to make sure that we don't have a lot of people without the disease in the studies and that we're looking at the right patient population.

In terms of using antibiotigrams as a means for linking up other organisms, another thing we've been looking at which is not sort of ready for prime time, but we've been looking at the use of biochemical fingerprinting, if you will, or profiles because labs generally are identifying organisms using commercially available strips, and organisms are given a particular score based on that and a probability of then being a particular organism.

I'm not saying they need to be identical scores, but the scores should be very close if you're essentially dealing with the same organism among things other than Staph. epi. And so for some kinds of organisms, I think, maybe these biochemical profiles and the scores they get on the commercially available identification strips might also be useful for telling you that you have the same organism.

CHAIRMAN CRAIG: Dr. Mermel.

DR. MERMEL: One other comment. I think

that I would bow to what's been raised. I guess the risk of contamination on a catheter, on a percutaneously drawn blood culture if it was a contaminated coag. negative Staph. rather than concordant with the catheter does seem to be compelling evidence to go beyond the antibiogram.

However, if you had blood cultures positive for coag. negative Staph., for example, over time that were positive, would you need the rigors of molecular fingerprinting? If you did a blood culture, positive coag. negative Staph., repeated a blood culture, again, a percutaneous draw several hours later again positive for coag. negative Staph., you let's say remove the catheter and that has coag. negative Staph.; so you've got multiple cultures over time, at least in the study that Sam referred to by Bates and Lee with their series of two articles in JAMA, multiple blood cultures over time was an independent predictor of true bloodstream infection.

CHAIRMAN CRAIG: Dr. Murray.

DR. MURRAY: I think what you do with the patient is one thing, but we're talking about evaluating a new drug, and I think you just want to be strict, and I think there's no reason these isolates can't be sent to a central laboratory and examined

post hoc.

So I think making all of the myriad of exceptions isn't the way to go for this purpose.

CHAIRMAN CRAIG: Okay. Dr. Raad.

DR. RAAD: Yes. I think there are two entities of Staph. epi., and I think this is what in our mind as clinicians there is this positive blood culture for Staph. epi. versus a situation which has been described here, which is catheter related Staph. epi. bacteremia where you have at least two positive blood cultures and a third positive culture which is a catheter culture.

In that setting, in our studies and the ones by Maki and colleagues and Mermel and colleagues, if you look at Staph. epi. with the same antibiogram from the catheter tip with at least two other positive blood cultures with the same antibiogram -- and this is not a restricted antibiogram, but more than one, vancomycin and trimetheprim sulfa and even others, rifampin; if you look at those antibiograms versus pulse electrophoresis, there is very good correlation that this is a true bacteremia and this is catheter originated.

So it would be ideal to do pulse gel electrophoresis, but whether this is achievable in a

study setting when you have 60 to even 120 or even 180 centers involved is another question.

I think that the other issue is with Staph. aureus, for example, where you have, again, the antibiogram is even more helpful or other organisms. If you have the same antibiogram from the catheter tip versus the peripheral blood, there seems to be reasonable correlation with a pulse gel electrophoresis from the data available on catheter bloodstream infections.

So I agree with Dr. Mermel. I think the pulse gel electrophoresis would be most helpful for Staph. epidermidis, but if you're really requiring multiple blood cultures with the same antibiogram, not just one single positive blood culture, and the same antibiogram from a catheter tip culture, you're talking about three cultures. This might be sufficient.

CHAIRMAN CRAIG: Dr. Archer.

DR. ARCHER: I think the problem with the antibiogram -- and I agree it can be useful -- is that you have to be very careful that the antibiotics that are being tested all have different resistance mechanisms. So looking at 6-beta lactems, for instance, doesn't help you.

so you have to be able to test susceptibilitytotetracycline, chloramphenicol, sulfa trimetheprim, which all have different resistance mechanisms and will help you define organisms that differ by a resistance gene, and a lot of labs don't do tetracycline, chloramphenicol susceptibility. So you don't have those.

And then you have the problem of inducability of some of these resistance phenotypes. You could have the same organism depending on how it's grown, and you may or may not induce resistance.

so I think the antibiogram, if done properly by somebody who knows what they're doing in probably a research lab, is probably helpful, but getting an automated susceptibility strip out, I don't know if that's going to be as useful.

And I think Barbara's point was an excellent one. You can batch all of these bugs. You can send them to a central lab, and so whether or not an individual hospital has pulse field capability or not is irrelevant in post hoc analysis.

CHAIRMAN CRAIG: Yeah, I agree with you, and I think that's the trend that I see happening all of the time anyway now, is that cultures are sent to a central lab.

Yes, Dr. Parsonnet.

DR. PARSONNET: It seems to me that the decision about this may depend on the type of study you're doing, whether you're doing a non-inferiority study or doing a superiority study, because if you're doing a non-inferiority study, I think you definitely have to do it because by not have post field gel electrophoresis, you have a lot of mush in the study and everything will look the same.

But if you're doing a superiority study, it may not be as important because you find a difference, and you've found a difference despite the randomness.

CHAIRMAN CRAIG: Any other comments on this?

At least I think the impression I got from the committee members was that for the coagulase negative Staphylococci, it's clearly a situation where post gel electrophoresis is required, but that antibiograms would be okay for Staph. aureus, Gram negative organisms like that.

Am I correct with everybody?

Okay. The next question is: give the importance of both clinical and microbiologic criteria defining the study population.

DR. CHIKAMI: Dr. Craig, before you move on --

CHAIRMAN CRAIG: Yeah.

DR. CHIKAMI: -- similarly as you dealt with the Part A of this question, it needs to sort of open it up to discuss the general issues of the clinical inclusion criteria. I think there were some comments about the other microbiologic --

CHAIRMAN CRAIG: I think that's what my next question is. How should microbiologic outcomes be assessed?

DR. CHIKAMI: All right.

CHAIRMAN CRAIG: And that's what I was going to get to.

So the last question is: given the importance of both clinical and microbiologic criteria to define the study populations and determine efficacy, how should microbiologic outcomes be assessed?

And we had a lot of discussion at the beginning where people were concerned about the use of hubcap cultures. We've heard about the infusate cultures, questions about that.

There's also questions about doing blood cultures at the end of therapy. So I think there are

a variety of issues that need to be reviewed under microbiologic definitions and also outcomes.

So, again, I'd like to readdress right at the beginning again, going back to what we're going to call microbiologic proof of a catheter related bloodstream infection, is to see if there are concerns again with some of those criteria that people think should be eliminated or modified in some form.

Dr. Weinstein.

DR. WEINSTEIN: Bill, I'm concerned about the Section 3 (b) for diagnosis. In the first sentence of that section it says, "When no obvious signs of inflammation at the catheter entry site are seen, the diagnosis of catheter related infection depends on either blood cultures drawn through the catheter or cultures of the catheter itself," and it makes no reference to peripherally obtained blood cultures, which I think are one of the keys.

So I think that needs to be addressed.

PARTICIPANT: Where are you?

DR. WEINSTEIN: Section 3(b) of the draft guideline, page 4. I'm sorry. It's Roman numeral three.

CHAIRMAN CRAIG: Yeah, I mean my interpretation of that was that the only way -- it

wasn't that that's criteria for cause that we're going to use for our definitions. I think they come later, but I think what they were trying to point out there, the only way of implicating the catheter as being the potential site of a bacteremia was either by drawing -- getting the organism from the catheter directly from rolling it or from cultures through it.

But I didn't think that they were implying then that you didn't need a peripheral blood culture for definition.

DR. ROSS: That's correct. Actually I think that that's a point that the way it's written, I agree. It may look as if we're saying that you don't need a peripheral blood culture, but actually as I said during my presentation, we'd actually advocate -- and this is in adults clearly -- two peripheral blood cultures.

But I agree absolutely that the diagnosis could not be established simply without a peripheral blood culture.

CHAIRMAN CRAIG: What I'd like people to focus on is on page 9 where we have the microbiologic criteria, and start with the top one and go right on down and see which ones people feel are appropriate and which ones they'd like to modify.

And the first one is having a concordant growth of the same organism from peripheral blood and a blood culture aspirated from a catheter as shown by quantitative cultures of catheter drawn and peripherally drawn blood cultures with a catheter to peripheral blood culture organism ratio of three to one to five to one regardless of pathogen.

Dr. Reller.

DR. RELLER: On the clinical criteria, we established or recommended a hierarchy so that localized signs of infection were given equal weight to temperature and one other component of SIRS, and temperature had primacy over the other components because that was a necessary criterion if one went that route.

And, similarly, I think there should be and believe that clinically there is a hierarchy in terms of confidence about the microbiological data, and the way I would do this is to require for the purposes of evaluation a new agent in a clinical trial for an evaluable patient, is to have a minimum of one peripheral blood culture and another independently obtained peripheral blood culture or a culture drawn through the catheter that implies independence of that other peripheral.

So that the idea would be two peripheral, independently obtained blood cultures and an alternative would be that second culture be drawn through an existing catheter, and that those organisms be the same **by** if they are coagulase negative Staphylococci, require pulse field gel electrophoresis, and if they are not coagulase negative Staphylococci, that they be shown to be similar either by biotyping biochemical reactions or extensive antibiogram.

And I think it needs to be defined because nowadays some of these isolates are monotonously similar in a given hospital in terms of their antibiogram, and a restricted antibiogram done for clinical purposes would not be sufficient, or that a whole lot of them have pulse field gel electrophoresis, which I think would be preferable.

But the emphasis is on that one would need for catheter related blood stream infections two positive blood cultures growing the same organism, one of which could be a catheter, and then all of these other things could by the sponsor be added on for the purpose of additional supportive data of the realness of that infection.

And I would delineate that it has to be,

you know, a semi-quantitative Maki culture if the catheter is removed because many of these catheters are not going to be removed. So I would put that in a second tier of evidence.

And then an individual sponsor may for the purposes of add-on scientific value, supporting information, give quantitative catheters of hubs, but I think that there is a distinct hierarchy in microbiological evidence, and I think all of this hub, catheter tip, quantitative, semi-quantitative, sonicated, not sonicated, electron microscopy and whatever is all interesting and possibly important for pathogenesis and supportive, but is not central to the evaluation of a given patient in relation to antimicrobial therapy for catheter relatedbloodstream infection.

CHAIRMAN CRAIG: I have a question for you. How would you tell primary bacteremia if you only got peripheral blood cultures from a catheter related infection?

DR. RELLER: Well --

CHAIRMAN CRAIG: Don't you have to get something from the catheter to be able to implicate the catheter? If you just got peripheral blood cultures, how would you be able to tell that from just

primary bacteremia?

DR. RELLER: Well, that's where all of those inclusion/exclusion criteria come in, Bill, plus the local. So you're talking --

CHAIRMAN CRAIG: No, I'm talking about pneumonia with bacteremia. I'm talking about primary bacteremia where you don't have another focus. The only way that you can implicate the catheter is to somehow get a culture from the catheter.

DR. RELLER: I don't agree with that, and I'll tell you why. I mean, if I have a coagulase negative Staphylococcus from two peripheral blood cultures and a patient is febrile who's got inflammation at the exit site of'the catheter, I do not believe that I have to draw blood through the catheter.

I mean it's a patient without a prosthetic valve, and I mean all of the other things that we have. I do not believe that one has to draw blood through that catheter to implicate the catheter in that kind of infection.

And I'd be interested to know from the NIH and Bob Banner's, you know, surveillance what you think about this issue.

CHAIRMAN CRAIG: No, but again, let me get